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TRAINING FOR THE PRACTICE OF AVIATION MEDICINE

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• *There is a definite need for special training for physicians to cope with the multitude of medical problems created by flight. Aviation medicine should be considered as an alloy composed of elements of several of the other basic medical specialties, such as ophthalmology, otolaryngology, psychiatry, internal medicine, and preventive medicine. In addition to the "family doctor" type of practice to flying personnel, there is the full-time specialized practice of aviation medicine, which includes consultants and investigators. To become a true specialist in aviation medicine one must undergo several years of graduate training.*

The seeds of aviation medicine were planted in the latter part of the 18th century, when man began to take to the air in balloons. Germination of these seeds, however, was delayed until the early part of the 20th century, when World War I accelerated the development and use of aircraft.

The need for special training for physicians, scientists, and aircrews to cope with the multitude of new medical problems created by flight was realized early in the 20th century. However, the first course of instruction in this new field of medicine, "The Basic Course for Flight Surgeons," was not offered until 1919 when the new School for Flight Surgeons was opened by the Army Air Service. One can say with reasonable accuracy that almost everything known about aviation medicine at that time could be taught in the three to four months allotted to this course. Although the field grew, slowly but steadily, between the two world wars, the length of the basic course remained relatively constant.

World War II boosted the growth of aviation tremendously and introduced the jet era. It also stimulated aviation medicine research and investigation. During the period of emergency, the basic course was shortened to six weeks. Its graduates were designated "aviation medical examiners" (A. M. E.) instead of "flight surgeons." To obtain the latter rating an apprenticeship of one year was, and still is, required.

By 1949 the store of aviation medical knowledge and the need for physicians with advanced training in this new field became so great that the U. S. A. F. School of Aviation Medicine initiated an additional academic year of aviation medical graduate education. This "Advanced Course in Aviation Medicine" was given to selected medical officers.

The Korean war and the "cold war," which followed in its wake, gave even greater impetus to the growth of aviation and opened the doors to the rocket age. Again it became evident that still more thoroughly trained medical specialists in aviation medicine were required to keep the medical service abreast of these developments. Therefore, in 1952 the Air Force program was lengthened and broadened by adding an academic year of preventive medicine and two years of residency training in aviation medicine. In the following year, aviation medicine gained official recognition as a medical specialty and the Air Force Specialty Training Program was adapted to that recommended by the certifying board in aviation medicine.

In 1954, with the concurrence of the board, two years of supervised practice were substituted for one of the years of residency training. In addition to at least one year of prerequisite training, the program now consists of a minimum of three years of formally organized and conducted training and of two closely supervised years of practice of the specialty.

The growth and development of educational programs in the new specialty of aviation medicine is depicted graphically in figure 1. Obviously it has been extraordinarily rapid. Consequently, I would like to consider this subject and to review briefly the first graduate educational program specifically designed to prepare a physician for the practice of aviation medicine as a specialty.

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Read before the 27th annual meeting of the Aero Medical Association, Chicago, April 18, 1956.

Educational Requirements

The "Essentials of Approved Residencies and Fellowships," published by the American Medical Association, and the bulletin of the American Board of Preventive Medicine on training requirements for certification in aviation medicine offer the specifications for the construction of training programs in the specialty of aviation medicine. Briefly, in addition to graduation from an approved school of medicine and completion of an approved internship, the following special education requirements must be met in order to become eligible for examination for certification in aviation medicine:

1. One year graduate study in preventive medicine in an accredited school of public health.

2. One year of graduate study in aviation medicine in an accredited school of aviation medicine.

3. At least one year of residency in aviation medicine.

4. Not less than one year of supervised practice of aviation medicine.

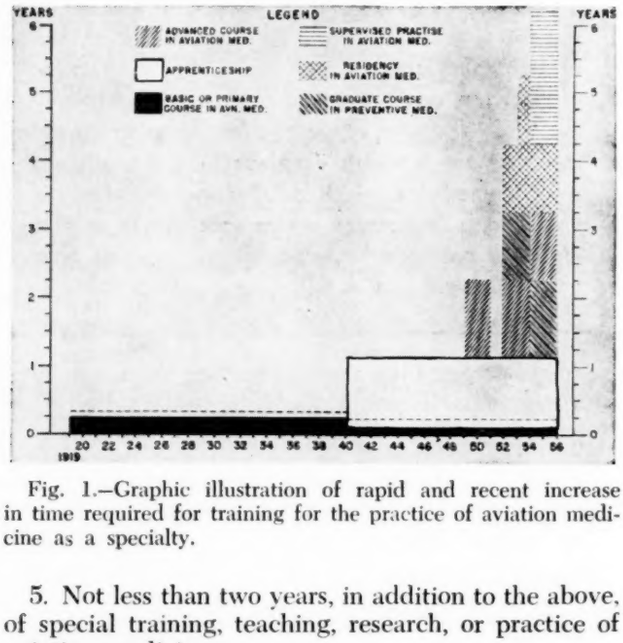
YEARS
LEGEND
ADVANCED COURSE IN AVIATION MED.
APPRENTICESHIP
BASIC OR PRIMARY COURSE IN AVN. MED.
SUPERVISED PRACTISE IN AVIATION MED.
RESIDENCY IN AVIATION MED.
GRADUATE COURSE IN PREVENTIVE MED.
YEARS
0 1 2 3 4 5 6
20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56
1919

Fig. 1.—Graphic illustration of rapid and recent increase in time required for training for the practice of aviation medicine as a specialty.

5. Not less than two years, in addition to the above, of special training, teaching, research, or practice of aviation medicine.

If a training program is compared to a building, these specifications could be said to indicate the number of floors which the building must have and the broad purpose of each floor. They, however, do not give any guidance on either the order in which these floors will be arranged or on the types of building materials which will be used in their construction. Any educational architect, therefore, in preparing plans for an aviation medicine specialty training program still faces many problems for which he must provide a solution. As indicated before, the Air Force program was constructed one floor at a time over a period of many years without the benefit of a blueprint for the final edifice. Consequently, during the past two years, it has been necessary to remodel a large part of the original building to better adapt it to its present purpose.

Problems and Solutions

In the operation of this program over the past four years, many problems have been encountered and, in the search for solutions, many lessons have been learned. These so-called solutions, however, are not considered to be the ultimate answer, and the program is constantly being revised and improved. Fortunately, the Council on Medical Education and Hospitals of the American Medical Association and the Board of Preventive Medicine recognize the need for flexibility at this early developmental stage and have encouraged such experimentation.

Definition.—In designing a training program for the specialized practice of aviation medicine, the first major problem encountered is the lack of a clear, universally accepted concept of aviation medicine as a specialty. When we asked various leaders in this field for their ideas on this subject, we found for example, that many of those with extensive experience and training in the clinical specialties—such as ophthalmology, otolaryngology, or internal medicine—considered aviation medicine primarily a clinical specialty; others, whose experience and training had been principally in preventive medicine, thought of it as a variation of that specialty; another group, which had been concerned most with its administrative and military aspects, regarded aviation medicine as an aerial version of military medicine.

In the preparation of our program we have considered aviation medicine as an alloy composed of elements of several of the other basic medical specialties such as ophthalmology, otolaryngology, psychiatry, internal medicine, and preventive medicine. We have insisted that it bears no more relation to military medicine than any other medical specialty in which training is conducted in a military environment or institution.

Many who agree on the nature or composition of aviation medicine seem to have difficulty in recognizing the role of the specialist in this field. For clarification of this point, one may divide the practice of aviation medicine into two types—the general practice and the specialized practice. Those engaged in the first type may be regarded as the "family doctors" of flying personnel. As such, they may practice aviation medicine on either a full-time or part-time basis. In preparation for this type of practice, a comparatively short postgraduate period of training has sufficed. In contrast, the specialized practice of aviation medicine is a full-time practice. Those engaged in this type of practice must be able to solve problems—as consultants or investigators—which are beyond the usual capability of the general practitioner of the specialty. Today, to acquire this level of knowledge and skill in aviation medicine one must undergo several years of graduate medical education to become a true specialist. It is for the latter type of practitioner that our Aviation Medicine Specialty Training Program is designed.

Objective.—The second major problem encountered in planning such programs is the establishment of the objective. Here, again, one is faced with a wide variety of opinions. Stated simply, the objective of this program is to prepare selected physicians, through intensive, specialized training, for employment—dependent

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upon their interests and talents—as aviation medicine consultants, researchers, and teachers and, after adequate experience, as directors or supervisors of aviation medicine programs conducted at any level.

Air Force Program

The four phases of the U. S. A. F. Aviation Medicine Specialty Training Program may be depicted as a multistaged rocket ship aimed at a career in aviation medicine. The entire program is built upon a background of a general medical education including an internship. The period of prerequisite training forms the launching platform. The academic year of graduate study in preventive medicine (phase 1) gets the program off the ground. The advanced course in aviation medicine (phase 2) provides added momentum and sets the course for the objective. In the residency year (phase 3) the program is given added thrust which will sustain the flight for a long time in the rarified upper stratosphere and space. The supervised practice years (phase 4), with a final, comparatively even output of energy, carry the trainee on a steady course to his objective.

Phase 1—The Graduate Course in Preventive Medicine.—If the specialty of aviation medicine is considered objectively, almost everyone will agree, first, that, as a separate discipline of medicine, it is concerned primarily with preventing accidents, illness, loss of effectiveness, and deaths due to flight; and, secondly, that it is more concerned with the problems of large populations than individuals. It is obvious, therefore, that any graduate education program and career in aviation medicine must be built upon an understanding of the fundamentals of preventive medicine. For this reason, the graduate course in preventive medicine constitutes the first phase of the program.

This academic year is provided at either the Johns Hopkins School of Public Health and Hygiene or the Harvard School of Public Health for Air Force trainees. Both of these schools have altered some of their courses and added other new ones to their curriculums in order to better present some of those aspects of preventive medicine which are applicable particularly to aviation medicine.

In both schools the student is offered an opportunity to qualify for a master of public health degree by taking certain required courses specified by the school. These account for approximately 50% of the total number of hours. In addition, Air Force students are advised to take specific "elective" courses which consume another 25% of the total available time. This is done in an effort to balance the educational fare offered by the two civilian schools, to insure that certain subjects are adequately covered prior to phase 2, and to avoid undesirable repetition and duplication of subject matter in the second year. A list of the more pertinent subjects offered our students in this year is shown in table 1.

Phase 2—The Advanced Course in Aviation Medicine.—Phase 2 is given at the School of Aviation Medicine, U. S. A. F., Randolph Air Force Base, Texas. In this second year of graduate study the student's attention is focused sharply on aviation medicine per se.

In the first six weeks all students are given flight indoctrination training with a class of flying cadets so that they may experience and better understand the psychological and physiological stresses of flight. They attend ground school and receive in-flight instruction in both conventional and jet aircraft.

During the remaining 10 months there is a thorough coverage of those parts of the basic sciences—such as physiology, biophysics, biochemistry, pharmacology, and psychology—which form the matrix of aviation medicine. A large portion of the time is spent on pure aviation medicine subjects such as the selection and classification of flying personnel; human engineering problems in aircraft; the planning, organization, and conduct of aircrew maintenance and effectiveness programs; rescue and survival training for aircrews; and the evacuation of patients by air. Students are shown how to apply the fundamental principles of preventive medicine learned in phase 1 to aviation medicine problems. Both didactic instruction and practical training are given in those clinical fields most closely related to aviation medicine. These include ophthalmology, otorhinolaryngology, neuropsychiatry, internal medicine, and traumatology. On well-organized, conducted field trips the students visit aircraft plants, civilian airline facilities, and military and civilian aviation test and research centers to observe aviation medical problems at their source and to study various types of aviation medicine programs and investigative studies designed to solve them. All students are given a brief

TABLE 1.—*Subjects Offered During Academic Year in Preventive Medicine (Phase 1 of Program in Aviation Medicine)*

Required Subjects
Principles of biostatistics
Principles of public health administration and practice
Principles of sanitation and sanitary engineering
Principles of epidemiology
Principles of public health microbiology
Ecology, biological and social (H)*
Elective Subjects
Principles of environmental and industrial health†
Physiological climatology† (JH)‡
Parasitic infections of man† (JH)
Forensic medicine†
Aviation medicine seminar† (H)
Principles of bacteriology and immunology† (H)
Human factors in industrial safety† (H)
Basic problems in industrial hygiene (H)
Human problems of adjustment in industry (H)
Industrial medicine practice (H)
Advanced epidemiology (H)
Analysis of population data
Analysis of data from special studies (H)
Practice of epidemiology (H)
Rickettsial and virus diseases (H)
Conservation of health in tropical countries (H)
Noninfectious mass disease and injury (H)
Military preventive medicine (H)
Hygienic aspects of ventilation (H)
Environmental physiology
General principles of audiology and speech (JH)
Chronic disease seminar (JH)
Statistical methods in epidemiology (JH)
Pathogenesis and pathology of neurotropic virus diseases (JH)
Mycology (JH)
Military mental hygiene (JH)
Elements of statistical analysis (JH)
Biological problems of control in virus diseases (JH)

† Elective courses which all U.S.A.F. aviation medicine students are required to take.
* H, Harvard School of Public Health.
‡ JH, Johns Hopkins School of Hygiene and Public Health.

course in effective oral and written communication. Also, a small portion of the curriculum is allotted to military medical subjects related to the practice of aviation medicine in the Air Force. The percentage of the total time given to each of the major subject areas is shown in figure 2. The relative amount of time and the actual number of hours of instruction devoted to each subject is depicted in figure 3.

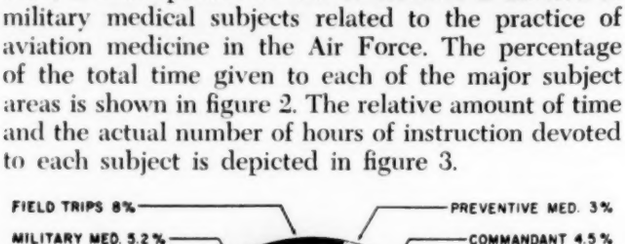

Fig. 2.—Percentage of total hours devoted to major subject areas in advanced course in aviation medicine.

Phase 3—Residency in Aviation Medicine.—During the year devoted to phase 3 residents are given an opportunity to apply the knowledge which they have acquired during the first two academic years to practical problems in all aspects of aviation medicine. Active participation with assumption of responsibility, rather than passive observation, is stressed.

Aviation medicine residencies are conducted under the auspices of the Tactical Air Command at Langley Air Force Base, Va.; of the Air Materiel Command at Wright-Patterson Air Force Base, Ohio; and of the U. S. A. F. School of Aviation Medicine at Randolph Air Force Base, Texas. The residency at Langley has the distinction of being the first one established in the specialty of aviation medicine. It was organized in 1952 by Brig. Gen. M. S. White, who is the surgeon of the Tactical Air Command and was one of the pioneers in aviation medical education. The second residency in aviation medicine was established in 1954 at Wright-Patterson Air Force Base under the leadership of Brig. Gen. Edward Tracy, who is the surgeon of the Air Materiel Command. The third residency was inaugurated in 1955 at the School of Aviation Medicine under the leadership of its late commandant, Brig. Gen. Edward Kendricks.

These senior medical officers are the directors of their respective residencies. As such, they furnish over-all guidance and supervision. Each program has a coordinator who is responsible for planning, scheduling, coordinating, and administering the residency program. The chiefs of the several services and divisions in which the residents receive training provide close supervision to each resident.

Langley and Wright-Patterson Residencies: The residencies at Langley and Wright-Patterson air force bases are organized in a very similar manner. As shown in figure 4, both 12-month programs are divided into three parts of equal duration. In the first division, the resident devotes his time to the clinical practice of aviation medicine; in the second, he participates in the practice of aviation medicine at the level of an air base; in the third, he practices the specialty at the level of a major air command. The titles which I have given to these divisions are similar, but not identical, to those used in each of the residencies. The ones which I use have been chosen because they are more easily identified with their civilian counterparts. For example, the "air base" level of aviation medicine practice in the military would correspond roughly to that at a civilian airport, a commercial airline base, or an aircraft manufacturing plant, and the "air command" practice would correspond to that engaged in by the medical director of a large commercial airline or an aircraft manufacturing company with several plants.

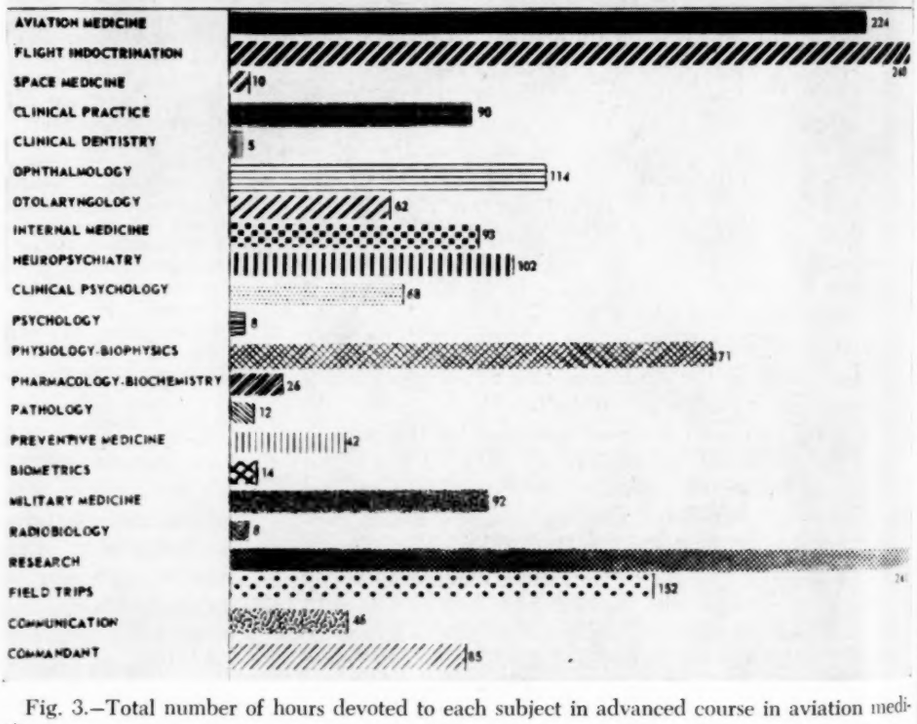

Fig. 3.—Total number of hours devoted to each subject in advanced course in aviation medicine.

The facilities and organizations used in the Langley program include the office of the surgeon of the Tactical Air Command, the base hospital and flight surgeon's office, a physiological training unit with a low-pressure chamber and its associated equipment, several local tactical fighter and fighter-bomber squadrons

equipped with a wide variety of aircraft, any of the numerous air bases of the command, and one of the largest research laboratories of the National Advisory Council on Aeronautics. At Wright-Patterson, use is made of the office of the surgeon of the Air Materiel Command, the base hospital and flight surgeon's office, several local flying squadrons and a flight test group equipped with a wide variety of aircraft, any of the several air bases of the command, the flight research center and its aeromedical laboratory, and the Kettering Laboratory in nearby Cincinnati.

Clinical Aviation Medicine Portion. The clinical aviation medicine training is conducted principally in the base hospitals and their outpatient clinics, including the base flight surgeon's office, by board-qualified specialists in aviation medicine, ophthalmology, otorhinolaryngology, psychiatry, internal medicine, general surgery, radiology, pathology, and several less closely related specialties. In electing the clinical specialties in which they wish to receive additional training, the residents are allowed considerable freedom but are encouraged to correct recognized deficiencies in those most closely related to aviation medicine.

Both hospitals are designated as aviation medicine specialty centers. As such, they serve as diagnostic and, if necessary, treatment centers for problem cases involving flying personnel and threats to their flying activities. These cases may include conditions with an obscure cause, such as episodes of vertigo, syncope, unconsciousness, hematemesis, transitory paralysis, angina, cardiac arrhythmias, and disorientation. They also may be diagnosed conditions such as spontaneous pneumothorax, early rheumatic heart disease, healed peptic ulcer, "arrested" tuberculosis, severe allergic rhinitis, and various types of visual impairment and deafness which require clinical studies, evaluation, and expert advice concerning the future flying status of the personnel. This consultation practice on such aviation medicine problem cases is potentially one of the most valuable portions of the residency training.

In the Langley hospital all aircrew inpatients are admitted to the aviation medicine service. When necessary they are referred or transferred to other specialty services for diagnostic assistance, care, and treatment. When this is completed, they are returned to the aviation medicine service for disposition and follow-up care. Aviation medicine residents, as members of the house staff, are responsible for these cases on both an inpatient and an outpatient status.

At Wright-Patterson, only flying personnel with illnesses or conditions peculiar to flying, such as dysbarism and aero-otitis, and those with aeromedical problem cases, referred for aviation medicine consultation, are admitted to the aviation medicine service as inpatients. Other aircrew inpatients are admitted directly to the specialized services as indicated by their clinical conditions. During their hospital assignments, aviation medicine residents are assigned to the aviation medicine service. On a consultant basis, they follow the clinical course of all aircrew patients in the hospital and "work-up" all patients referred for aviation medicine consultation. In addition, they rotate to the other specialty services in which they elect additional training.

This inpatient portion of the resident's training presents certain problems for which we have no true solutions. It is not known whether it is best to admit all aircrew inpatients to the aviation medicine service and to refer, or transfer, them to other specialized services only when necessary for consultation or treatment beyond the capability of the aviation medicine specialists (as is done at Langley) or to admit them to another specialized service and follow their course only as consultants on the aviation medical aspects of their conditions. I tend to favor the latter. However, I am convinced that all patients with conditions peculiar to flying and all aircrew members referred for consultation as having aviation medical problem cases should be admitted to the aviation medicine service on either an inpatient or an outpatient basis, for only by this procedure can proper training be provided in the clinical aspects of aviation medicine.

In this phase of the program there also is considerable variation in opinion in regard to the amount of time which should be devoted to clinical training. Here

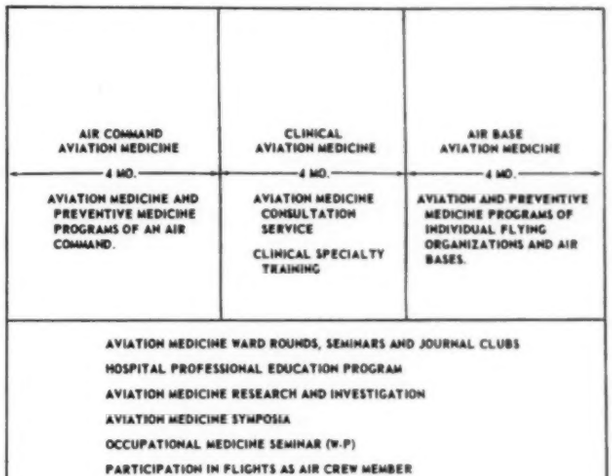
AIR COMMAND AVIATION MEDICINE
4 MO.
AVIATION MEDICINE AND PREVENTIVE MEDICINE PROGRAMS OF AN AIR COMMAND.
CLINICAL AVIATION MEDICINE
4 MO.
AVIATION MEDICINE CONSULTATION SERVICE
CLINICAL SPECIALTY TRAINING
AIR BASE AVIATION MEDICINE
4 MO.
AVIATION AND PREVENTIVE MEDICINE PROGRAMS OF INDIVIDUAL FLYING ORGANIZATIONS AND AIR BASES.
AVIATION MEDICINE WARD ROUNDS, SEMINARS AND JOURNAL CLUBS
HOSPITAL PROFESSIONAL EDUCATION PROGRAM
AVIATION MEDICINE RESEARCH AND INVESTIGATION
AVIATION MEDICINE SYMPOSIA
OCCUPATIONAL MEDICINE SEMINAR (W-P)
PARTICIPATION IN FLIGHTS AS AIR CREW MEMBER
FIELD TRIPS

Fig. 4.—Principal divisions of aviation medicine residency programs of the Tactical Air Command (Langley Air Force Base) and the Air Materiel Command (Wright-Patterson Air Force Base).

again we find the conflict between those who view aviation medicine primarily as a clinical specialty and those who view it primarily as a preventive medical specialty. Initially, in the Air Force program we have tended to side with the latter and have endeavored to maintain a balance in favor of the preventive side without neglecting the important clinical aspects. I believe that, after we have had more experience, we may give greater emphasis to clinical aspects during the residency year.

Air Base Aviation Medicine Portion. The air base aviation medicine portion of the residency is built around the aviation medicine outpatient clinic (base flight surgeon's office) and emphasis is given to the aircrew effectiveness programs of the base and individual flying units. During this period the residents conduct the aircrew effectiveness programs of the flying units to which they are assigned, provide consultation on aviation medicine problems referred to them,

and sharpen their diagnostic acuity and therapeutic skill in the closely allied clinical specialties by working in those clinics. In the Wright-Patterson program, this training is given in a separate four-month period; at Langley it is combined with the clinical aviation medicine training into one eight-month period.

In both programs, clinical training is enhanced by participation in other portions of the hospital's professional education program, in aviation medicine seminars and journal clubs, and in aviation medicine symposiums, conducted quarterly in turn at each of the residency sites.

Air Command Aviation Medicine Portion. In the air command aviation medicine portion the resident is given an opportunity to participate in the conduct and supervision of the aviation medicine and preventive medicine programs of a large command composed of many Air Force units and bases. During this period under supervision his duties are as follows:

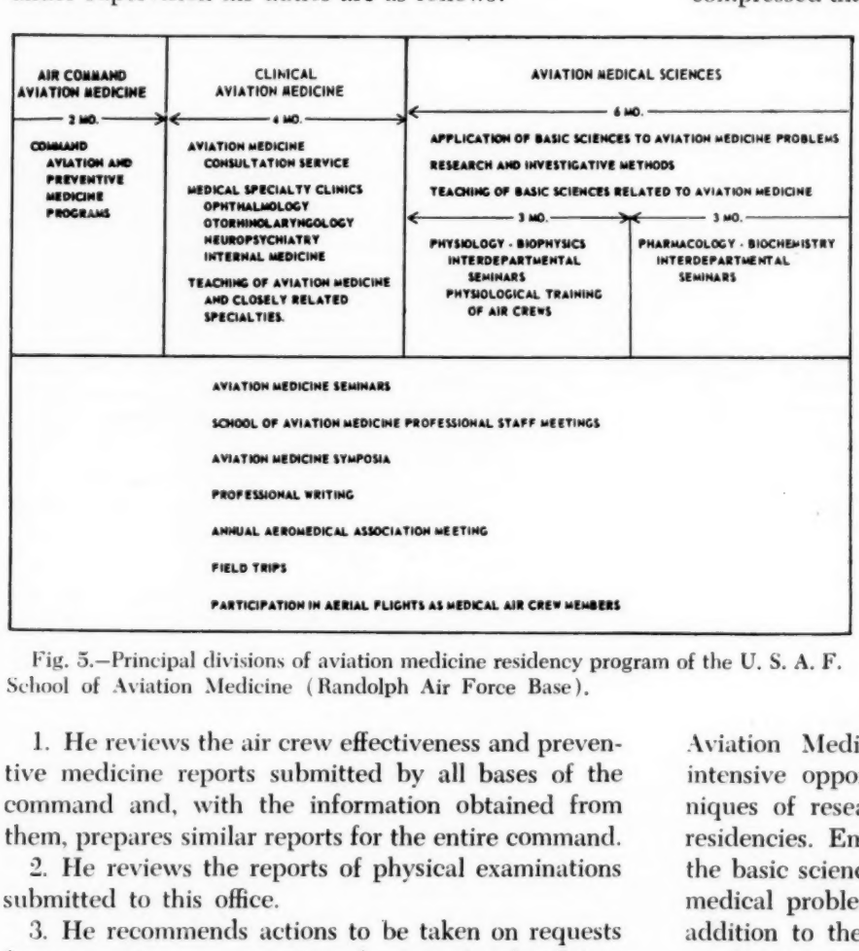

Fig. 5.—Principal divisions of aviation medicine residency program of the U. S. A. F. School of Aviation Medicine (Randolph Air Force Base).

1. He reviews the air crew effectiveness and preventive medicine reports submitted by all bases of the command and, with the information obtained from them, prepares similar reports for the entire command.

2. He reviews the reports of physical examinations submitted to this office.

3. He recommends actions to be taken on requests for suspension or revocation of suspension for flying.

4. He accomplishes liaison in regard to aviation medicine problems within the headquarters and with other Air Force and non-Air Force agencies.

5. He makes staff studies of the aviation and preventive medicine programs of subordinate bases and provides consultation service to them on problems referable to these medical specialties.

6. He assists in the establishment of policies and the preparation of command directives related to aviation and preventive medicine.

School of Aviation Medicine Residency: In September 1955, a third Air Force aviation medicine residency was established, at the School of Aviation Medicine, U. S. A. F. Although this residency has the same purpose and objectives as the other aviation medicine residencies, its program is organized differently in order to take advantage of several unique opportunities which the school can offer (fig. 5). In comparison with the other residencies, greater emphasis is placed on basic sciences, investigative procedures, teaching, and the consultative practice of aviation medicine. Much less time is devoted to unit, base, and command aircrew effectiveness and preventive medicine programs.

Air Command Portion. The air command portion of the school's residency program is conducted under the supervision of the crew training air force surgeon, whose headquarters is at Randolph Air Force Base. The training offered during this period is similar to, but more compressed than, that of the other residencies.

Clinical Portion. In the clinical aviation medicine portion the resident assumes more closely the role of a "fellow." As such he acquires the responsibility for all aviation medicine problem cases referred to the school for consultation and participates in the studies conducted on the patient in each clinical department. When all studies are completed, he prepares a clinical brief and presents the case with his recommendations to the staff. In addition, he participates as an instructor in the several aviation medicine courses conducted by the school. Also, he is given an opportunity to increase his knowledge and proficiency in the closely allied specialties by working in any of the clinics conducted by the departments of ophthalmology, otorhinolaryngology, neuropsychiatry, and internal medicine.

Medical Science Portion. The medical science portion of the School of Aviation Medicine residency offers a much more intensive opportunity for familiarization with techniques of research and investigation than the other residencies. Emphasis is given to the application of the basic sciences to the solution of practical aviation medical problems which have arisen in the field. In addition to these investigative activities the resident participates in regularly scheduled interdepartmental seminars on subjects related to aviation medicine.

In approving of the residency program of the school, we were fully aware of its somewhat radical departure from the previously established pattern. This action was thought justifiable on an experimental basis. It is anticipated that it, like the others, will be modified in several respects as additional experience is acquired. It is believed very desirable to have at least one residency with such rich opportunities in aviation medicine for training in teaching and investigation so that officers

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who have demonstrated interest and ability along these lines can be given an early opportunity to mold their career to those channels.

Phase 4—Supervised Practice of Aviation Medicine.—During this final phase of the Aviation Medicine Specialty Training Program, the officer is given an opportunity to apply the theories, fundamentals, and principles of aviation medicine, which he has been taught during the first three phases, to the practice of the specialty under close, expert supervision. An extensive experience in all aspects—preventive, clinical, investigative, and administrative—is offered for a period of one to two years. In a few selected cases, the second year of this phase may be spent in a fellowship which provides additional experience in research and/or teaching in aviation medicine or in a closely related scientific field; in a year of residency or fellowship in a clinical specialty closely related to aviation medicine; or in a special assignment which would enhance the person's training in a particular aspect of the specialty.

In the majority of these supervised practice assignments, the officer is given the duties and responsibilities of the chief or assistant chief of the aviation medicine and preventive medicine divisions in the office of the surgeon of a major command or air force. There also are a few assignments in which he may be given an opportunity to practice aviation medicine through research and/or teaching duties and responsibilities. These provisions give the program additional flexibility and permit early channeling of an officer's training into the field of aviation medicine practice in which he has manifested interest and capability.

In table 2 are listed some examples of the duties which officers perform during these supervised practice assignments on the staffs of command surgeons. This experience would be comparable to that which one in a civilian program might receive as an assistant to the medical director of an airline or of a large aircraft manufacturing company.

In addition to conducting the advanced course in aviation medicine (phase 2) and one of the residency programs (phase 3), the School of Aviation Medicine also is responsible for the operational support of the first three years (phases 1 through 3) of the program. This consists of the coordination of all three years to eliminate undesirable repetition, of providing budgetary support, and of rendering advice and guidance upon request. The aviation specialty training program as a whole is supervised by the surgeon general.

In September, 1956, 20 medical officers were graduated from the complete U. S. A. F. Aviation Medicine Specialty Training Program; a total of 27 were enrolled in the first three phases of the program; and an additional 11 were in the supervised practice phase.

Summary

Within the framework of the standards and essentials for education and training established by the Council on Medical Education and Hospitals of the American Medical Association and the Board of Preventive Medicine, the Air Force Medical Service has organized and conducted the first complete education and training program leading to certification in aviation medicine. In so doing, many knotty and perplexing problems pertaining to the definition and practice of aviation medicine as a specialty and to the objectives, content, organization, and conduct of the program as a whole have been encountered. The solutions that have been developed may not prove to be the final, true solutions, but experience to date suggests that the program is on the right track and that it is basically sound.

TABLE 2.—*Principal Types of Duties Performed During Supervised Practice Phase (Four) of Aviation Medicine Program*

As chief or assistant chief of aviation medicine in a major air command
1. Plan, organize, coordinate, and supervise aviation medicine program of entire command
2. Act as consultant in aviation medicine for entire command
3. Review all base aircrew effectiveness and medical flight reports (where required), prepare the consolidated command report, and initiate any corrective action indicated
4. Evaluate health status of command aircrew personnel and recommend measures to correct any problems
5. Investigate and recommend corrective measures for aviation toxicological problems
6. Participate in command flying safety program
7. Review all aircraft accident reports and initiate any action indicated to prevent recurrence of any human factors that may have contributed to the accident
8. Investigate and coordinate with proper staff agencies problems involving procurement, evaluation, proper use, and maintenance of personal flying equipment
9. Evaluate all medical equipment used in aeromedical operations
10. Investigate aeromedical problems created by all types of aircraft assigned to the command
11. Participate in regular and frequent aerial flights as an aircrew member in all types of aircraft flown by command and render necessary reports on observations
12. Inspect, evaluate, and recommend improvements in medical portions of base crash rescue plans
13. Prepare training programs in first-aid measures for instruction of air and ground crews, crash rescue teams, emergency vehicle drivers, and other appropriate personnel
14. Inspect, evaluate, and assist in command physiological training and aircrew physical fitness programs
15. Review all unusual problems involving physical qualifications for flying and recommend proper action
16. Plan and supervise the command aeromedical research program
17. Keep abreast of aeromedical research by reviewing publications, attending conferences, and visiting the School of Aviation Medicine, the aeromedical laboratory, and other appropriate military and civilian aeromedical research centers
18. Maintain records on all aviation observers (medical), flight surgeons, and aviation medical examiners assigned to the command
19. Participate in military and civilian medical meetings and, when requested, speak on subjects pertaining to aviation medicine
20. Make regular staff visits to command bases to
    (a) Gain first hand knowledge of local professional, aeromedical, and aircrew problems
    (b) Conduct aeromedical seminars for all aviation medical examiners, flight surgeons, flight nurses, and other interested staff members in order to
        (1) Disseminate new aeromedical knowledge
        (2) Promulgate newly established aeromedical policies and procedures
        (3) Encourage maximum effectiveness and devotion to duty of assigned medical officers on flying status
        (4) Further develop the *esprit de corps* of the flight surgeons of the command
        (5) Increase medical officer enrollment in the aviation medicine training programs

As chief or assistant chief of preventive medicine in a major command
1. Plan, organize, coordinate, and supervise the preventive medicine program of entire command
2. Act as consultant in preventive medicine to entire command
3. Advise base preventive medicine officers in regard to
    (a) The investigation and control of outbreaks of communicable diseases and related problems such as environmental sanitation, industrial medical problems, insect and rodent control, food service sanitation, housing, waste disposal, and personal hygiene
    (b) The study and control of noninfectious mass disease and injury problems
4. Review all base preventive medicine reports, analyze and prepare consolidated command preventive medicine reports including recommendations for corrective actions
5. Review preventive medicine publications, attend conferences, and keep abreast of preventive medicine research and developments
6. Initiate research and investigative projects in practical problems in preventive medicine arising within the command
7. Maintain liaison and coordinate activities with other military, government, and civilian authorities and agencies
8. Maintain appropriate statistical data and charts depicting the morbidity and mortality rates for all conditions affecting the health of the command
9. Prepare and promote education and training programs for the prevention of illness and improvement of the health of the command
10. Make regular and frequent staff visits to command bases to observe and assist local preventive medicine programs

Addendum

Since this article was written, the aviation medicine residency conducted at Langley Air Force Base has been discontinued and the one conducted at the U. S. A. F. School of Aviation Medicine at Randolph Air Force Base has been increased proportionately.

Figures 1, 3, and 4 were supplied by the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D. C.

EMERGENCY SERVICE WITHIN THE HOSPITAL

Carolyn H. Ziegler, M.D.
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• *When respiratory difficulties develop in a hospital patient, the anesthesiologist should be called promptly. Emergency kits should be kept ready at all times in a central location. This report analyzes 100 consecutive cases in which anesthesiologists were called for help in emergency rooms, the nursery, the radiology department, and the medical and surgical wards of a 600-bed university hospital. The cause of the respiratory difficulty was neurological disease in 54 cases, poisoning or drug reactions in 17, cardiac disease in 11, and metabolic disturbances in 6. Among the neurological cases the most frequent trouble was cerebrovascular accident (21 cases) and head injury (10 cases). The insertion of an endotracheal tube was the most important method of treatment, and was carried out in 80 patients; positive pressure assistance of respiration with oxygen was required in 28. No reliance was placed on drugs as analeptics or respiratory stimulants; it is believed that this type of treatment is less than useless. Of the 100 patients in this series, 4 were dead when the anesthesiologist arrived, 14 died during the initial treatment, and 45 improved but died later as a result of their basic disease. Thirty-seven patients who had been in serious difficulty were saved by prompt calls for assistance and by the efficient use of emergency equipment.*

Resuscitation is a field with which every physician should be familiar. Acute cardiovascular and respiratory problems may be an immediate threat to the life of the patient. The management of these emergencies may tax the skill of an expert and often requires training greater than that of the average intern or resident. Assistance in the management of these problems, ideally, should be promptly available within the hospital.

The nature of the practice of anesthesiology is such that acute respiratory and circulatory problems are commonly seen and treated in the operating room. The anesthesiologist is usually in the hospital; he has the equipment, and he is both available and skilled in the techniques of resuscitation. He should, therefore, be called upon to assist in the treatment of those patients who develop acute respiratory or circulatory difficulties.

The role of the anesthesiologist in certain specialized types of respiratory problems has been discussed by others. O'Brien [1] and his co-workers described the part which the anesthesiologist may play in the treatment of the respiratory difficulties of poliomyelitis patients. An excellent survey of the various methods of infant resuscitation has been presented by Cook and associates.[2] Holinger [3] discussed the role of the laryngologist in the resuscitation of the newborn infant. These particular situations are important, but they give no idea of the frequency or wide variety of emergencies which occur in a general hospital.

This paper is based upon the resuscitation experiences of the department of anesthesiology in a 600-bed university hospital. Both the attending staff and the house staff know that prompt assistance in emergencies is available upon telephoned request. During the day a large group of anesthesiologists may be drawn upon for emergency calls. At all other times three trained individuals are in the hospital. Several emergency kits are in readiness at all times in a central location. These are equipped with endotracheal tubes, airways, laryngoscopes, drugs, needles, syringes, and a device for giving artificial respiration with oxygen (see figure).

Calls for assistance average one or two per day. In most instances the emergency calls involve problems of acute respiratory obstruction or depression. Occasionally, profound circulatory collapse is the major problem. In many instances there are combined difficulties. The anesthesiologist takes full charge of the immediate management of the acute respiratory problem and gives advice as to future treatment with regard to tracheotomy and the use of respirators and resuscitators. Return visits are made as frequently as necessary for the individual patient. A special record card is provided on which the data pertaining to the call are noted: patient's name; room number; hospital number; primary diagnosis; state of consciousness; condition of airway; blood pressure; pulse; treatment; and results of treatment.

In this paper we shall discuss 100 consecutive patients who had acute respiratory difficulties and for whom the department of anesthesiology was called for consultation and assistance in resuscitation. All these occurrences took place outside of the operating, delivery, and recovery rooms. Emergency calls were received from the emergency rooms, nursery of newborn infants, radiology department, and medical and surgical wards of the hospital. The age range of patients attended was from a few minutes to 86 years. The basic disturbances responsible for the emergency calls and the results of treatment are indicated in table 1.

Eighty-two per cent of the patients were comatose. The lesions most commonly encountered were disturbances of the nervous system, including cerebrovascular accidents, head injuries, cerebral edema after craniotomy, meningitis, epilepsy, cerebral metastasis, poliomyelitis, and tetanus. The cause of difficulty in the next most common cases was poisoning due to overdosage or idiosyncrasy to drugs. These reactions are enumerated in table 2. Cardiac and metabolic dis-

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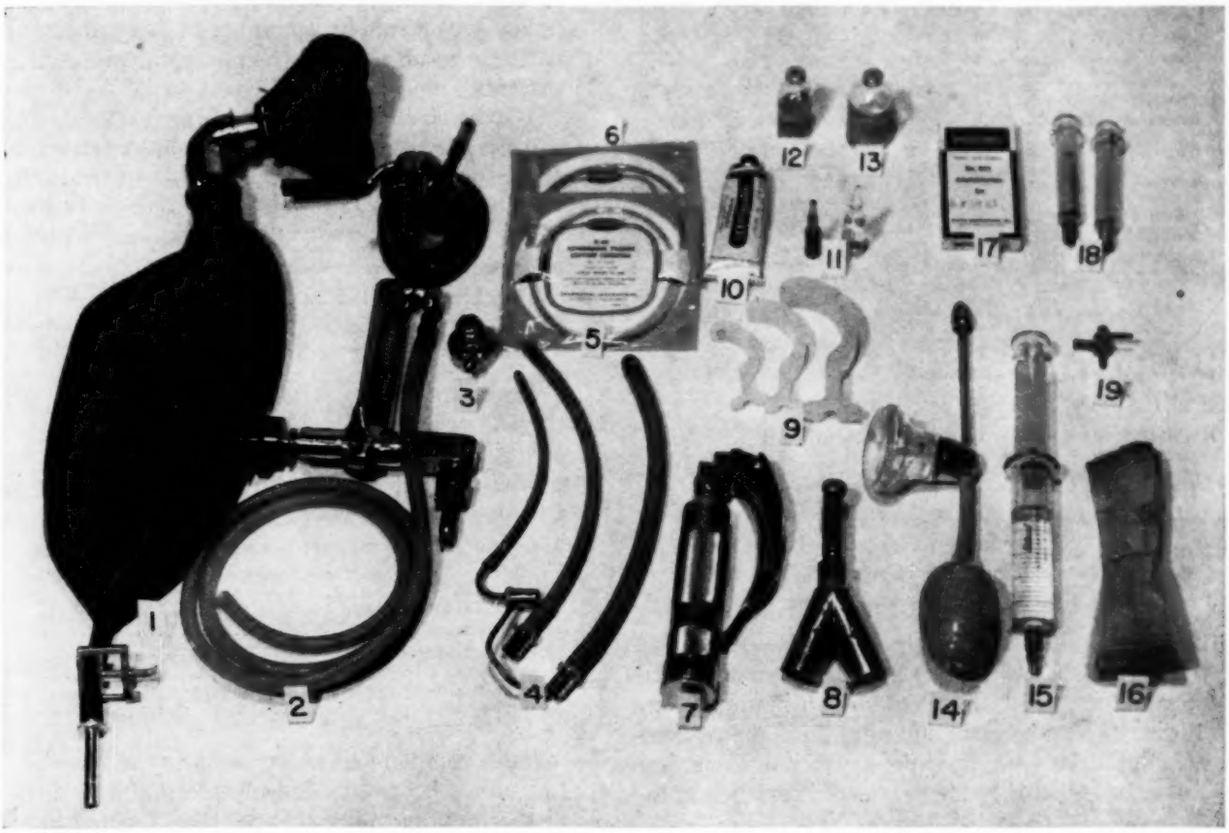
eases contributed 11 and 6 cases respectively. The types of respiratory difficulties are indicated in table 3. The types of treatment given are indicated in table 4.

Treatment

The insertion of an endotracheal tube was the most important method of treatment. This was done in 80 patients for the purpose of establishing an airway so that pulmonary ventilation could take place. In 84 instances the respiratory passages required cleansing with a suction catheter. Oxygen was administered to 98 patients, and of these 29 received positive-pressure assisted respiration. In 18 instances other medication was administered, including aminophylline, barbiturates, nalorphine hydrochloride, hexamethonium bromide, helium, isoproterenol (Isuprel) hydrochloride, and digitalis. Bronchoscopy was necessary to clear the airway in two instances and was performed by the anesthesiologist. Cardiac massage was done twice by members of the surgical service.

Carbon dioxide was not used in any instance. The old experimental work, which showed that carbon dioxide played a part in the control of respiration, led to the erroneous belief that it should be used as a respiratory stimulant. Every individual constantly produces carbon dioxide as a metabolic waste product. In all patients with respiratory difficulty an excess of carbon dioxide is present, and the aim of therapy is to decrease the acidosis, as well as to provide oxygen.

Carbogen (a mixture of 5% CO_2 and 95% O_2) was used intermittently at the request of the attending physician for one patient who had carbon monoxide poisoning. The rationale for its use in this instance is that the chemical affinity of hemoglobin for carbon monoxide is said to be decreased in the presence of acidosis, thus increasing the speed of excretion of carbon monoxide. Schwerma and associates [4] have demonstrated in animal experiments that oxygen-carbon dioxide combinations have no superiority over oxygen alone and, furthermore, that carbon dioxide-oxygen mixtures tend to increase the acidosis already present, so that it may actually do harm to the patient.



Equipment in emergency kit: (1) breathing bag and masks; (2) oxygen flowmeter; (3) endotracheal tube adapter; (4) endotracheal tubes; (5) suction catheter; (6) oxygen catheter; (7) laryngoscope; (8) adapter for gas machine; (9) oral airways; (10) anesthetic ointment; (11) vasopressors; (12) succinylcholine; (13) atropine solution; (14) atomizer with local anesthetic agent; (15) 2.5% thiopental (Pentothal) sodium; (16) sterile needles, (17) tubing for intravenous administration; (18) syringes; and (19) three-way stopcock.

Goodman and Gilman [5] state that the dissociation of carboxyhemoglobin is greatest in the presence of pure oxygen.

Comment

The treatment of shock due to injury, blood loss, or cardiac disease is well understood by members of the hospital intern and resident staff and usually is well managed. On the other hand, the treatment of respiratory disturbances is too often misunderstood. Many physicians still rely upon the subcutaneous administration of stimulant or analeptic drugs, which are of little value even when given intravenously and which are of no value and even may be harmful if the airway is

obstructed. When one considers the delay incident to obtaining the drugs, the slowness of absorption from subcutaneous sites, and the general inadequacy of these drugs in serious conditions, it is clear that this type of treatment is less than useless. Indeed, reliance upon drugs introduces delays in therapy which may well be fatal to the hypoxic or the asphyxiated patient.

TABLE 1.—*Etiology of Acute Respiratory Difficulty*

	Cases, No.	Dead On Arrival	Died During Treatment	Improved, Then Died of Basic Disease	Recovered
Neurological disease	54	3	5	29	17
Cerebrovascular accident	21	2	1	15	3
Head injury	10			5	5
Posteraniotomy difficulty	7		2	4	1
Bulbar poliomyelitis	2			2	
Epilepsy	2				2
Quadriplegia	2				2
Meningitis	2		1	1	
Fever (convulsions)	2				2
Miscellaneous	6	1	1	2	2
Poisoning and drug reaction	17	1		1	15
Cardiac disease	11		3	7	1
Metabolic disturbances	6		1	5	
Uremia	3			3	
Hepatitis	2			2	
Diabetes	1		1		
Miscellaneous	12		4	3	5
Peritonitis	1		1		
Perforated ulcer	1				1
Burn	1			1	
Carcinoma of pancreas	1		1		
Postoperative debility	1			1	
Pulmonary insufficiency	1			1	
Tracheobronchitis	1				1
Bleeding peptic ulcer	1		1		
Leukemia	1				1
Infant—aspiration of food	1				1
Hyaline membrane disease	1		1		
Tracheal compression	1				1

In most instances of respiratory disturbance it is necessary to provide a clear airway and to remove secretions, vomitus, blood, or other foreign material from the upper respiratory tract and often from the tracheobronchial tree. It is usually necessary to provide oxygen and often to give assisted or artificial respiration to the patient, until his brain has sufficiently recovered from hypoxia so that the respiratory center may again initiate and maintain adequate spontaneous respiration.

TABLE 2.—*Poisonings and Drug Reactions*

	Cases, No.
Carbon monoxide	3
Tetracaine (Pontocaine) hydrochloride	3
Barbiturates	2
Meperidine (Demerol) hydrochloride	1
Salicylates	1
Atropine	1
Picrotoxin	1
Boron hydride	1
Smoke	1
Bromidism	1
Diatrizoate (Hypaque) sodium	1
Unknown	1
Total	17

Frequently, at the time of arrival of the anesthesiologist, the situation may look hopeless. Nevertheless, prompt, skilled, and persistent attention to the patient results in an appreciable salvage rate. Of the 100 patients mentioned in this paper, 4 were dead at the time the anesthesiologist arrived and 14 died during the initial treatment; 45 patients improved with therapy but died later as a result of their basic disease. Thirty-seven patients recovered from the immediate difficulty and also completely recovered from the basic disturbance. When one considers the serious condition existing at the time, this represents a surprisingly high survival rate. The salvage rate can undoubtedly be improved by early recognition of respiratory difficulty and prompt calling of the anesthesiologist for assistance. These calls should be made by the first person (nurse, aide, or orderly) who sees the trouble and before the intern or the resident or attending physician is notified. This policy will result in a number of false alarms, but it will also result in saving the lives of some seriously ill patients.

TABLE 3.—*Types of Respiratory Problems*

	Cases, No.
Tongue and soft-tissue obstruction	57 (6 conscious)
Convulsions	16 (3 conscious)
Apnea	12 (2 conscious)
Aspiration	8 (2 conscious)
Decreased pulmonary ventilation	7 (4 conscious)
Total	100

Summary

In the emergency service of the department of anesthesiology in a 600-bed hospital, emergency calls have averaged one or two per day. Of 100 patients who required assistance, 82 improved with treatment. Forty-five patients died later of their basic disease, and 37 made a complete recovery and left the hospital. That the survival rate was unexpectedly high is attributed to the fact that other services have learned to call for assistance promptly. It is suggested that in all institutions the anesthesiologist be called more frequently and more promptly to assist in managing respiratory difficulties.

TABLE 4.—*Types of Treatment*

	Cases, No.
Endotracheal intubation and oxygen	80
Oxygen by mask and breathing bag	18
Suction of air passages	84
Total receiving oxygen	98
Miscellaneous: cardiac drugs, vasopressors, sedatives, ganglioplegics	21

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ROLE OF BED REST IN TREATMENT OF RHEUMATIC FEVER

REVIEW OF LITERATURE AND SURVEY OF CURRENT OPINIONS

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• *Sixteen specialists in rheumatic fever independently contributed opinions as to the role of bed rest in the treatment of this disease. None were able to cite adequate, long-term, well-controlled studies comparing the course of patients whose treatment had included a rigid regimen of bed rest with the course of patients who had been given more liberty. None had made such a controlled study themselves, and three indicated that they had no experience with treatment other than strict bed rest. None felt that they had seen evidence that the known ill-effects of absolute bed rest on other types of subjects tended to delay recovery in patients with rheumatic fever, but several mentioned the emotional effects of strict bed rest. The most decisive criterion for allowing increased activity was stated as (1) subsidence of the acute debilitating symptoms, by five physicians; (2) downward trend of laboratory signs, by five other physicians; and (3) disappearance of all signs of inflammatory activity and freedom from recurrence of symptoms after cessation of steroid and aspirin therapy, by six physicians. All agreed that they would prescribe absolute bed rest in acute rheumatic fever with manifestations of arthritis and carditis with heart failure, but differed as to the strictness and duration of the bed rest in the absence of heart failure or signs of carditis. There was a diversity of opinions as to the hypothetical case of a patient with inactive rheumatic fever, an organic apical systolic murmur, and no cardiac enlargement, but eight physicians stated that they would allow all normal activity except for competitive sports.*

For many years, rest has been the keystone of treatment of acute rheumatic fever as well as many other diseases. Limitation of physical activity in varying degrees has also been considered of paramount importance in the convalescent stage. At the present time, the concept of importance of strict rest in many types of illnesses is undergoing revision. In the management of tuberculosis, for example, the emphasis on strict bed rest is decreasing in the presence of new methods of therapy. This is true also in many febrile illnesses. Even in the treatment of coronary thrombosis, bed rest is being replaced by the "chair treatment." It seems, therefore, that the importance of rest, in both the acute and convalescent phases of rheumatic fever, needs reevaluation. In those rheumatic patients under treatment with cortisone or corticotropin (ACTH) in whom all signs of inflammation appear to be suppressed, the role of rest is not clear. It seemed of value, therefore, to report a review of the literature in regard to bed rest in rheumatic fever. In addition, it was decided to poll the opinions of a group of authorities in the field from the United States, United Kingdom, and France, thereby providing some data as to what is currently considered good management in this regard in various centers in the United States and abroad.

Review of the Literature

It is of interest that rest was not considered of great importance in the early writings concerning rheumatic fever. It is probable that this was due in part to the fact that the diagnosis of rheumatic fever as an entity was usually not well established and that the possibility that carditis might be present in a subclinical form in cases of polyarthritis was not fully appreciated. For instance, Earp,[1] in 1909, in discussing 12 patients with acute rheumatism, reported that none were confined to bed for more than 10 days. Two of the patients probably had acute carditis. However, a few years later the emphasis upon prolonged and strict bed rest had become accepted. Scott,[2] in 1915, stated that bed rest was the most important aspect of therapy and suggested that the duration of the rest be influenced by the severity of the disorders such as arthritis, carditis, chorea, and anemia. He also advised a prolonged convalescence and believed that even after recovery unusual activity or excitement might cause a new attack in the rheumatic individual. Although no objective data were presented at the time to support the belief that rest was of extreme importance, the opinion has continued to prevail, with very few exceptions, up to the present time.

Strict Bed Rest.—No good controlled studies are available to either support or deny the opinion of the importance of rest. Most authors rely on personal experience to support their belief that absolute bed rest is of paramount importance in acute rheumatic fever. Practically all articles discussing the therapy of rheumatic fever outline very much the same conservative regimen, with a few notable exceptions. The intensity with which bed rest was recommended probably reached its peak during the 1920's, as exemplified by Raven's [3] recommendations in 1924. At that time, Raven suggested complete bed rest until signs of rheumatic activity had subsided and advised increasing physical activity by only 15 minutes daily during the convalescent period. Sheldon's [4] advice in 1938 is still frequently quoted. He also suggested that absolute

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rest is essential and that even those patients with unrecognized carditis should have a minimum of one month of complete rest.

In more recent review articles [5] on the therapy of acute rheumatic fever, the same opinion is held in regard to both therapy in the acute phase of the disease and that in the convalescent stage. Bed rest has been listed as a time-honored treatment by these authors for the following reasons: 1. It decreases the work of the heart and thus prevents impending heart failure or perhaps aids the recovery from failure that is already present. This view has recently been challenged in the comparison of "chair treatment" with bed rest in other cardiac disorders.[6] 2. It may play a role in preventing permanent cardiac damage. For instance, Raven [3] states that in his experience progressive involvement of the heart may occur unless prolonged rest is prescribed. 3. It shortens the course of the rheumatic process. Although no controlled studies seem to be available to support this fact, many authors such as Cahall [5a] believe that rest does shorten the course of the disease. Cahall compares rheumatic fever with tuberculosis, stating that the primary purpose of rest in both diseases is to render the process inactive. Black [7] has stated that "everyone has seen exercise increase the extent of the infection if the rheumatism is not in the quiescent stage." 4. It may prevent recurrences. Black [7] believes he has seen many relapses or recurrences when activity was increased two to three months after the onset of the disease. This point does not seem well documented.

Only one clinical study has been found which might provide support for the opinions listed above. Kurtz [8] reported on a series of 96 patients treated with an extremely conservative regimen with absolute rest during the entire period of rheumatic activity. The program of convalescence was also a very gradual regimen. The results were interpreted as showing only 3 of the 96 patients, or 3.1%, developing any conclusive evidence of new or increased valvular deformity. Unfortunately, the first-attack cases were not listed separately, and there was no true control group or long-term follow-up.

Conservative Treatment.—In general, even in the armed forces during World War II, a fairly conservative approach was usually taken in treatment of acute rheumatic fever during the active stage, although the approach to the convalescent phase was considerably more radical.[9] However, Robertson and co-workers [9a] reported their experience with 200 rheumatic patients in the Army in whom early ambulation was used. They felt that the evidence in favor of strict rest had not been absolutely established and that the anxiety neuroses which developed (particularly in young males in the armed forces) suggested that considerably more harm than good might be done both physically and mentally to the individuals by enforcing a strict regimen. It was their impression that bed rest was often not the ultimate in achieving maximum rest. More freedom on the ward allowed more actual rest by promoting physical comfort and emotional relaxatio-

The patients were permitted some physical activity within the first 24 hours if physical discomfort did not prohibit it. Such activity was allowed even in cases of active carditis if heart failure was not present. Dyspnea or fatigue was used primarily as a guide to the maximum activity that was desirable. Physical activity consisted essentially of bathroom privileges, sitting in a chair, and walking about the ward as desired. During the subsiding stage of the disease, the patients also walked outdoors. Unfortunately, no definite statistics are given, particularly in terms of residual cardiac damage. However, it was believed that the rheumatic process itself subsided just as rapidly as in patients on a regimen of strict bed rest.

Since acute rheumatic carditis has never been reproduced experimentally, it has not been possible to use the experimental approach to either prove or disprove the time-honored concept of rest therapy in acute rheumatic fever. A few studies tend to point out some of the ill effects of bed rest. Harrison [10] demonstrated that in heart failure pulmonary edema tends to occur more readily if the patient is in the recumbent position. In his study with Thomas,[11] using rats in which myocardial damage had been produced by thermal injury to the left ventricle, there was a considerably higher mortality in those rats whose physical activity had been limited than in those who had been allowed to limit their own activity. In recent studies in rheumatic fever, Johnston [12] presented evidence that prolonged bed rest influences adversely the retention of nitrogen and calcium. Very moderate degrees of activity offset this.

The recommendations for rest in the convalescent period have shown a less conservative approach in the last few years, although there is still considerable disagreement in this regard. Taran [13] has for many years been a proponent of the use of the sanitarium for convalescent care. It has been his impression that recovery is more rapid and the incidence of recurrence lower with a prolonged convalescence in the sanitarium. It is interesting to note, however, that in recent years [5c] he has been recommending a shorter period of convalescence than the 8 to 10 months recommended in 1943.[13b] There has been a growing appreciation of the fact that the heart is damaged, as time passes, not by ordinary physical activity but by progressive inflammation of the rheumatic process itself aggravated by recurrences.[14]

Rehabilitation.—Most authors are now impressed with the medical and physical invalidism that has resulted from overemphasis upon physical rest in the convalescent period. This fact was well established in the armed forces during World War II. In the Navy [9b] and in the Army Air Forces,[15] a physical training and vocational rehabilitation program was arranged for the convalescent period to demonstrate to the patient (prior to his returning to duty) that he was able to carry out rigorous exertion without difficulty. Once evidence of rheumatic activity had disappeared, the patient was moved rapidly through a program of increasing activity that was finally comparable to full duty. The Navy experience seemed to

show that a period of approximately nine weeks of gradually progressing physical activity was usually sufficient.

The War Department memorandum, published in 1944,[16] seems worthy of review since it now has stood the test of time. It reads as follows: "Physical activity after recovery: The patient who has made a satisfactory recovery from rheumatic fever can be assured, once he is physically fit, that limitation of physical activity is not helpful in protecting against additional attacks of subsequent heart disease and, therefore, is not indicated. It is important that this be made clear because the concept is so widely held that limitation of activity is essential in any condition which has any relation to cardiac injury."

For the individual with inactive rheumatic fever, limitation of physical activity often has been prescribed for many years. Although it has been suggested in the past that normal physical activity may lead to recurrences or to progression of heart disease, this has little support when considered in the light of our present knowledge regarding the role of streptococcic infections. Progression of heart disease is probably due to either smoldering rheumatic activity or recurrences. It is generally advised that no limitation of physical activity be placed upon the child who recovers from his initial attack with no evidence of valvular heart damage. For the individual who has residual valvular lesions, there is more disagreement in regard to the effects of physical activity. However, the present trend in this regard is to allow the individual to restrict his own activity.

In the armed forces,[15] it was shown that most individuals with early rheumatic heart disease have no loss of cardiac reserve and are capable of as much physical exertion as a normal person. Eisenberg and co-workers [5b] showed that the results of exercise-tolerance tests at a children's camp for inactive cardiac patients did not differentiate between children with rheumatic heart disease and normal children. Cardiac intolerance was seen only in those children with congenital heart disease. He also found no correlation between cardiac enlargement and exercise tolerance. After 20 years' experience with children with inactive rheumatic heart disease, it was Eisenberg's impression that children who show exercise intolerance have an active rheumatic process. He believes that each child seeks or reaches that level of play which is comfortable and gratifying. The real danger to such a child is not play or exercise but recurrent streptococcic infection. Gibson [17] agrees that children with rheumatic valvular disease should be allowed to exercise without restriction, although they should stop short of actual fatigue. He is impressed that one obtains much better cooperation with such recommendations, since the child who is being constantly nagged will become rebellious and do exactly what is forbidden.

Survey of Opinions

A survey was conducted among a group of authorities in the field of rheumatic fever practicing in leading medical centers in the United States, United Kingdom, and France regarding their present opinions of the role of bed rest in rheumatic fever therapy. Specific questions concerning the use of absolute bed rest (confined to bed 24 hours per day), modified bed rest (allowing bathroom privileges, sitting in chair, walking about the ward), and limited activity (confined to house with rest periods in the morning and afternoon) were included in a questionnaire which each was requested to answer. Of 20 physicians contacted, 16 replied.

In the following paragraphs are the questions asked and a tabulation of the opinions expressed in response to each question.

1. Are you aware of any good reports (involving such material as long-term follow-up studies and information on adequate controls) on the evaluation of absolute bed rest in active rheumatic fever? Of the 16 physicians replying, none were aware of controlled studies. Reference was made to follow-up studies of a limited nature which tended to suggest a better outcome in patients treated with a rigid regimen of bed rest.

2. What briefly is your experience as regards residual cardiac damage in patients with active rheumatic fever treated with absolute or modified bed rest in comparison with limited activity? Six physicians felt that they had no evidence that a rigid regimen is better than limited activity as regards residual cardiac damage. Three indicated that they had had no experience with treatment other than absolute bed rest and hence did not wish to express an opinion. Seven held the opinion that bed rest tends to prevent residual cardiac damage. The following clinical evidence was cited by them: First, follow-up studies have seemed to indicate better results in those treated with bed rest. Second, progressive cardiac enlargement has occurred in some patients not kept on bed rest. Third, the fact that one-half of the patients with rheumatic heart disease cannot give a history of rheumatic fever might indicate that bed rest makes the difference. Most of the physicians indicated that the prevention of recurrence of rheumatic fever was probably a more important factor in preventing residual cardiac damage than the factor of bed rest.

3. Have you any evidence that the ill effects of absolute bed rest, i. e., negative nitrogen balance, loss of calcium, and psychological invalidism, contribute to a more prolonged course of the disease? None felt that they had any good evidence that this was a factor in prolonging the organic course of the disease. Several expressed the opinion that the emotional effect of strict bed rest was an important factor in the total welfare of the patient, however.

4. If you confine your patients with active rheumatic fever to absolute bed rest, what are your criteria for allowing increased activity? Five physicians increased the patient's activity as soon as the acute debilitating symptoms, i. e., fever, malaise, arthralgia, and heart failure, subside. Five would increase activity when a downward trend of such laboratory signs as the sedimentation rate and C-reactive protein level was es-

tablished. Six would wait until all signs of inflammatory activity (i. e., absence of symptoms, normal sedimentation rate and mucoprotein value, disappearance of C-reactive protein) had disappeared after therapy with steroids or aspirin was stopped before allowing increased activity. Several of those questioned indicated that they tend to be more liberal with activity than they were several years ago.

5. Given a patient with acute rheumatic fever with manifestations of arthritis and carditis with heart failure, what rest program would you advise? All indicated they would prescribe absolute bed rest. Given a patient with arthritis and only mild carditis without failure, what rest program would you advise? Twelve would prescribe absolute bed rest. Four would allow modified bed rest. Given a patient in whom the disease was seemingly limited to the joints with no evidence of carditis, what rest program would you advise? Eleven would prescribe absolute bed rest (although for a shorter period). Three would prescribe modified bed rest, and two would allow limited activity.

6. Given a patient with inactive rheumatic fever who has an organic apical systolic murmur with no cardiac enlargement, what activity would be advised? Would competitive sports be allowed? Seven would impose no limitation (several of these suggested waiting 12 months before allowing competitive sports). One would limit activity for one year and restrict competitive sports for two years after the attack. Eight would allow all normal activity except for competitive sports. One of these physicians stated that, although he does not advise competitive sports, he did not feel certain that this restriction should be imposed.

Summary

In a review of the literature and a questionnaire survey of specialists in rheumatic fever, no objective proof was found to indicate that strict bed rest is necessary for a satisfactory convalescence in acute rheumatic fever. In spite of this lack of objective proof, most workers in the field, including those authorities questioned, hold the opinion that maximum rest is still an important aspect of the therapy of active rheumatic fever, these opinions being based on clinical impression. In the presence of carditis, most physicians feel that absolute bed rest is indicated. Also most agree that bed rest should be continued until all or most of the signs of activity have disappeared.

However, many authorities are beginning to question the necessity of strict programs and are tending to liberalize rest regimens, allowing earlier ambulation at the present time than several years ago and allowing more activity during the convalescent period. This is thought to result in less emotional trauma to the patient. It is generally agreed that the patient with inactive rheumatic fever should not be drastically restricted in his activity. Of the authorities questioned, all agree to allowing normal activity, although approximately one-half of these would prohibit competitive sports in the presence of a residual murmur.

A controlled study of different rest regimens with long-term follow-up has not yet been made. This would be very difficult to carry out and would require many years to complete, but it might yield important objective information concerning the role of bed rest in rheumatic fever.

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The specialists who replied to questionnaire in survey of opinions concerning bed rest in rheumatic fever were Rachel Ash, M.D., Boston; Edward E. Fischel, M.D., New York; Stanley Graham, M.D., Glasgow; R. S. Illingsworth, M.D., Sheffield, England; John D. Keith, M.D., Toronto, Canada; Vincent Kelley, M.D., Salt Lake City; Ann Kuttner, M.D., New York; Jacqueline Labesse, Paris; Hugh McCullough, M.D., Chicago; Currier McEwen, M.D., New York; Benedict F. Massell, M.D., Boston; Milton Saslaw, M.D., Miami Beach, Fla.; B. E. Schlesinger, M.D., London; Leo M. Taran, M.D., Roslyn, N. Y.; A. G. Watkins, M.D., Cardiff, England; and May Wilson, M.D., New York.

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CHRONIC THYROIDITIS AND AUTOIMMUNIZATION

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• *An explanation of chronic thyroiditis in man was sought in observations made on rabbits, dogs, guinea pigs, and human subjects. The rabbits received injections of saline extracts of rabbit thyroid glands. The tests for circulating autoantibodies utilized the phenomena of precipitation, complement fixation, and tanned-cell hemagglutination. The third of these, based upon the principle of altering the surface of the red blood cells by dilute tannic acid so that they absorb proteins, was particularly sensitive. The three tests were applied to serums from 35 rabbits injected with rabbit thyroid extract, and thyroid autoantibodies were found in 32. Structural damage was found in the thyroid roughly in proportion to the autoantibody titer in the serum. Similar studies were carried out in dogs and guinea pigs with canine and guinea pig thyroid extracts respectively. The three tests were then applied to serums from patients with chronic thyroiditis. Twelve such patients were found whose serums contained circulating antibodies specifically directed against extracts of human thyroid glands. Three typical case histories are given, with histological findings on thyroid tissue removed during surgery. Six other patients with chronic thyroiditis, proved histologically, were not found to have autoantibodies in their serums at the time of study. These findings lead to the hypotheses that some types of chronic thyroiditis are related to an autoimmunization process within the patient against his own thyroid tissue, and that thyroid autoantibodies are at once indicators and links in the chain of pathological processes.*

For many years only foreign proteins were considered to be true antigens. Horse serum, for instance, proved to be a powerful antigen when injected into human beings, but it did not elicit antibody formation when injected into horses. Conversely, human serum injected into horses elicits antibodies to human serum, but its failure to act as an antigen when injected into humans constitutes the basis of the therapeutic usefulness of human plasma and human albumin. Landsteiner's discovery of the human blood groups revealed the fact that agglutinins directed against blood group factors within the human race but not within the same individual are present in human serums. Such antibodies have been called isoantibodies. Ehrlich and Morgenroth succeeded in producing isoantibodies in goats by injecting certain goats with red blood cells of other goats, thus producing immune isoantibodies. Attempts to immunize goats against their own red blood cells, however, did not succeed. The inability to produce antibodies against constituents of one's own body was interpreted by Ehrlich as the expression of a biological law referred to by him as "horror autotoxicus." Our ever-increasing knowledge of isoimmunization is based upon the recognition of the refusal of the living body to produce autoantibodies.

In recent years the pathogenesis of several diseases has been ascribed to an interaction between supposed autoantibodies and antigens present in the tissues. Most conspicuous among a number of diseases in this category are certain blood dyscrasias, frequently referred to as "autoimmune blood diseases." Several observations, indeed, seem to support this concept, such as the positive direct Coombs test in acquired hemolytic anemia. The experimental evidence, however, is still incomplete. Yet there are several known instances where autoantibodies have been produced experimentally, such as by the injection of brain tissue. Rabbit brain, for example, when emulsified in Freund adjuvants and injected into rabbits, after an incubation period of a few weeks, will frequently lead to damage in the animal brain referred to as allergic encephalomyelitis.[1] The nature of the antigen involved here is not quite clear but according to some investigators it is a proteolipid. Recently Freund and co-workers [2] have produced aspermatogenesis in guinea pigs by immunizing them with spermatozoa of the same species.

A protein known to be specific for the organ from which it is derived is thyroglobulin, as described by Hektoen, Fox, and Schulhof [3] in 1927. More recently, even crude thyroid extracts have been found to produce antiserums that are specific for thyroid extract, presumably due to their high thyroglobulin content.[4] Because of the unusual immunological position of thyroglobulin, we tried to test the validity of Ehrlich's "horror autotoxicus" law in this case by injecting experimental animals with thyroid extract of their own species.

From the departments of bacteriology and immunology (Drs. Witebsky and Rose), pathology (Dr. Terplan), and surgery (Drs. Paine and Egan), the University of Buffalo School of Medicine and the Buffalo General Hospital.

Experimental Studies in Animals

Rabbits.—Saline extracts of rabbit thyroid glands were prepared as has been described in detail in previous publications.[5] The immunization procedure consisted of the injection of 0.05 ml. of an emulsion containing equal parts of the thyroid extract and Freund adjuvants (mixture of mineral oil and Arlacel [main ingredient, mannide mono-oleate], containing killed Mycobacterium butyricum or M. smegmatis) into each of the footpads of the rabbits. In some instances, a second and even a third set of intradermal injections of 0.1 ml. of antigen emulsion into each of four sites on the back of the rabbit was given. Dogs and guinea pigs were treated in essentially the same manner, using pooled thyroid extracts of the respective species.

For the demonstration of circulating antibodies, three major serological procedures were used: (1) precipitation, (2) complement fixation, and (3) tanned-cell hemagglutination. The precipitation test, carried out by mixing undiluted rabbit serum with serial dilutions of thyroid extract, though positive in some instances, proved to be the least sensitive technique. In addition, nonspecific precipitation was occasionally observed, when mixtures of thyroid extract and normal rabbit serum were allowed to stand for longer periods of time, such as overnight at 4 C. The complement fixation test, performed in the manner previously described,[6] was more successful in our hands. Nineteen out of 50 rabbits studied (38%) were positive. The tissue specificity of the complement-fixing antibodies was examined by testing them with normal rabbit serum and with saline extracts, prepared in the same manner as the thyroid extracts, of the following rabbit organs: liver, spleen, pancreas, heart, lung, kidney, and adrenal. None gave any significant reaction, in contrast to the thyroid extract, which fixed complement even in high dilutions. In a later phase of our investigations the tanned-cell hemagglutination test was also used. This test, introduced by Boyden,[7] is based upon the principle of altering the surface of red blood cells by diluted tannic acid so that they absorb proteins. Coated tanned cells are then agglutinated specifically by antibodies directed against the protein used for coating. Of 35 serums of rabbits injected with rabbit thyroid extract examined by this technique, 32 (91%) revealed the presence of thyroid antibodies, in some instances exhibiting titers 10 to 100 times as high as those obtained when tested by complement fixation.

In order to study further the organ specificity of antiserums obtained by injecting rabbits with rabbit thyroid extracts, the rabbit antiserums were tested with thyroid extracts prepared from more than 20 individual rabbits. All thyroid extracts when examined either by complement fixation or hemagglutination reacted principally alike. In some instances, the thyroid gland was removed from the rabbits before immunization with pooled thyroid extract was initiated. Antiserums produced in this way, when examined serologically, gave equally strong reactions with extracts of the thyroid gland from the antibody-forming animal itself. The antigenicity of extracts of the thyroid gland for the same individual rabbit was further investigated by subjecting rabbits to total thyroidectomy and injecting them with an extract of their own thyroid gland. Of 15 rabbits treated in this way, the serums of 4 were positive on complement fixation tests, and 7 out of 10 gave positive hemagglutination reactions with rabbit thyroid extract, proving the potential antigenicity of the thyroid extract for the same rabbit.

After rabbit thyroid extracts were found to be antigenic for the rabbit itself, the question arose as to which constituent of the crude thyroid extract was responsible for immunization. Purified rabbit thyroglobulin was prepared in our laboratory by Dr. Sidney Shulman, by carefully using ammonium sulfate precipitation.[8] By ultracentrifugal criteria, the preparation contained 88% thyroglobulin. Thyroglobulin was injected into the footpads of six rabbits in the usual manner. Antibodies were demonstrable in some of the animals three weeks after injection. Two months after injection the animals were killed, and their serums were examined for the presence of rabbit thyroid antibodies by means of the tanned-cell hemagglutination test. Table 1 shows the agglutination observed after the tubes remained overnight at 4 C.

All six rabbits had developed antibodies against rabbit thyroid extract after a single set of intradermal injections of a total of only 0.1 ml. (0.27 mg.) of purified rabbit thyroglobulin. It might be added that two of the six rabbit serums (419 and 422) also contained complement-fixing antibodies. These findings pointed to thyroglobulin as the constituent of rabbit thyroid extract responsible for immunization of rabbits against rabbit thyroid extract.

As previously reported,[9] injection of crude rabbit thyroid extract causes damage to the thyroid gland of the antibody-producing animal itself. We then wondered to what extent the immunization with purified thyroglobulin brought about comparable changes,

TABLE 1.—*Data on Agglutination of Thyroid-Coated Human Erythrocytes by Serums of Rabbits Immunized with Purified Rabbit Thyroglobulin*

Dilutions of Rabbit Serum	Rabbit No.*					
	417	418	419	420	421	422
1:5	++++	+++	++++	+++	+++	++++
1:10	+++	+++	++++	++	+++	++++
1:20	+++	+++	+++	++	+++	+++
1:40	+++	++	+++	++	+++	+++
1:80	++	++	+++	++	++	+++
1:160	++	++	++	−	++	+++
1:320	+	+	++	−	++	++
1:640	−	−	++	−	−	+
1:1,280	−	−	++	−	−	+
1:2,560	−	−	++	−	−	−
1:5,120	−	−	−	−	−	−

* Normal rabbit serum gave negative reaction in all dilutions.

and, therefore, the thyroids of immunized rabbits were examined histologically. The rabbits were exsanguinated, and the thyroids were removed, fixed in buffered formaldehyde, and stained with hematoxylin and eosin. The extent of distinct structural changes seemed to correlate roughly with the antibody titer. Typical examples of varying degrees of such changes are seen in figures 1 and 2. Figure 3 shows the thyroid gland of an animal (rabbit 410) injected with rabbit serum instead of rabbit thyroglobulin and depicts the normal thyroid pattern. The findings in this rabbit served as a control.

Sections of the thyroids of these two rabbits, 417 and 419 (fig. 1 and 2), showed various degrees of disruption of the colloid follicular pattern. The cellular infiltrations between the follicles consist of lymphocytes, eosinophilic leukocytes, and plasma cells. The eosinophilic cells are especially prominent in the capsule. In the more intensely and diffusely inflamed thyroid of rabbit 419 there is slight fibrosis and a few nodules consisting of lymphocytes. The histological changes in the thyroids of rabbits immunized with isolated rabbit thyroglobulin are similar to those in rabbits immunized with whole thyroid extract, as previously described.[5]

Dogs.—In addition, four dogs received in all four footpads an initial series of intradermal injections of dog thyroid extract incorporated into Freund adjuvants. One animal developed a strong circulating thyroid antibody that was demonstrable by complement fixation. It died suddenly, and no autopsy was performed. The other three dogs showed no circulating

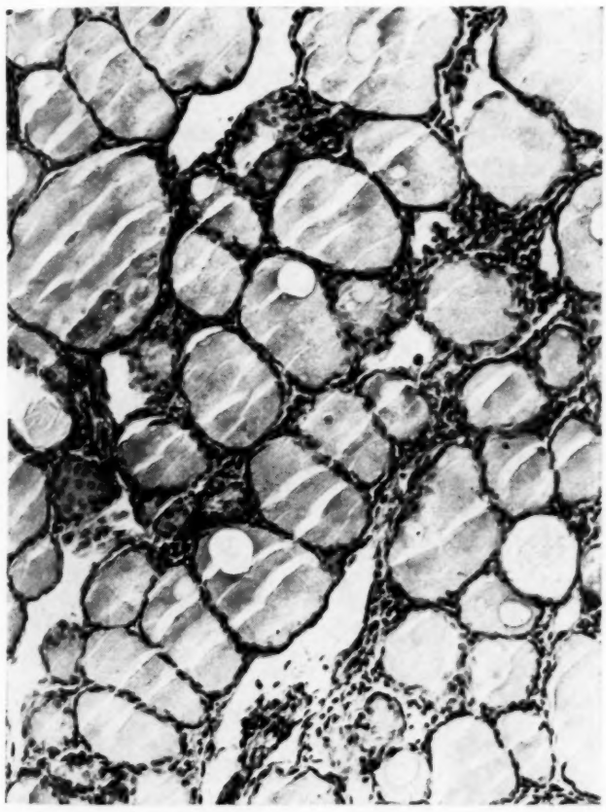

Fig. 1.—Photomicrograph of section of thyroid from rabbit 417, which had been injected intradermally with 0.2 ml. of rabbit thyroglobulin and Freund adjuvants on Jan. 6, 1955, showing infiltration between acini filled with colloid. Some epithelial desquamation in intimate connection with interstitial infiltration can be seen in several areas. Rabbit was killed on March 29, 1955 (× 190).

antibodies and were reinjected intradermally into the skin of the back twice, each time a total of 0.4 ml. being given in four different sites. At the end of nine months, still no circulating antibodies of significant titer were demonstrable. The dogs were then killed. On postmortem examination, the thyroid glands of all were found to be hard and small.

Dog 1184: The dog was given an intradermal injection of 0.4 ml. of a pooled crude dog thyroid extract on Sept. 20, 1954, with 0.5 ml. with Freund adjuvants added (omitting acid-fast bacilli) on Dec. 24, 1954, and with 0.5 ml. with Freund adjuvants on Jan. 28, 1955. On May 23, 1955, the dog was subjected to thyroidectomy. At the time of operation, the dog weighed 26 lb. (11.8 kg.), and the left thyroid weighed 0.4 Gm. and the right thyroid 0.6 Gm. On histological examination, the entire lobe of the thyroid was found to be diffusely infiltrated by lymphoid cells, here and there more densely arranged, forming ill-defined nodules, and numerous disintegrating leukocytes. The acini were diminished and contained very thin colloid or leukocytes, desquamated epithelium, and lymphoid cells. Most of the original acinar pattern was completely masked by the dense cellular infiltrations. In addition, there was distinct increase of collagenous fibers and a striking change of the original colloid follicles to small or even solid follicles, with prominent epithelium and vacuolated cytoplasm. Such areas contained little or no colloid and resembled solid parenchymatous proliferations of thyroid epithelium. The interstitial inflammatory changes were most marked in the periphery and seemed to extend into the capsule of the thyroid, in which distinct fibrous thickening was noticed. The leukocytic infiltration of the more solid parenchymatous areas was as prominent as that in other fields of the thyroid where some acini were still preserved (fig. 4).

Evidently, changes of considerable extent occurred in the thyroids of the dogs. We might conclude, therefore, either that severe damage to the thyroid glands after injection with thyroid extracts can occur, even in the absence of demonstrable antibodies in the serum, or that the circulating antibodies in these dogs were absorbed by the remaining thyroid tissue at the time the blood was drawn. A study on a second series consisting of nine dogs was started about a year ago, and the series is still under observation. Circulating thyroid antibodies are at present demonstrable in seven of these dogs.

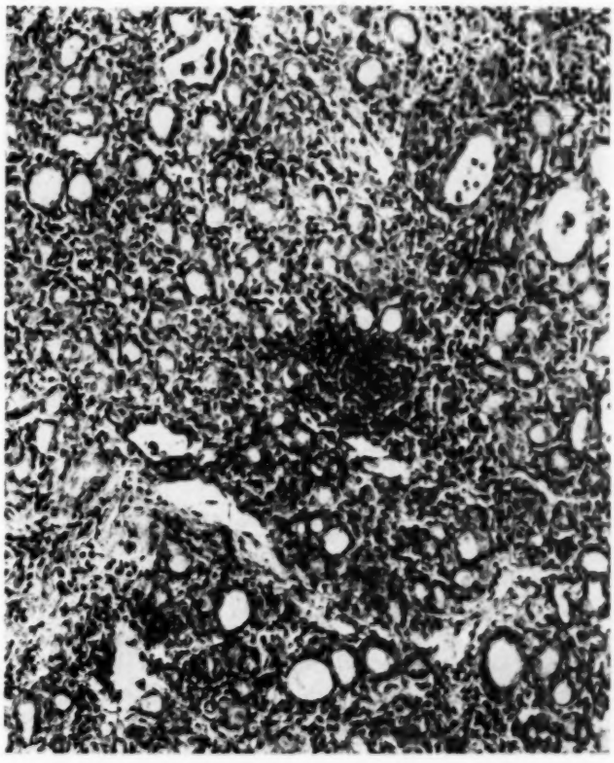

Fig. 2—Photomicrograph of section of thyroid from rabbit 419, which had been injected intradermally with 0.2 ml. of rabbit thyroglobulin and Freund adjuvants on Jan. 6, 1955, showing more marked changes than those in figure 1. Acini of thyroid are small and contain only thin colloid. In the lumens of some are desquamated cells. Interstitial tissue between them and the edematous capsule is densely infiltrated by lymphocytes, plasma cells, and, especially in the periphery of the gland, by numerous eosinophils. There are a few nodular accumulations of lymphocytes, a slight focal fibrosis in the subcapsular portions, surrounding few small colloid follicles is also noticeable. Animal was killed on March 14, 1955.

Guinea Pigs.—Histological changes in the thyroids of guinea pigs, basically similar to those in rabbits and dogs, have also been observed after injections with thyroid extract from guinea pigs. Circulating thyroid antibodies were found in some instances, but none of

the guinea pigs produced antibodies as strongly as did the rabbits, and these circulating antibodies have been demonstrated so far only by the tanned-cell hemagglutination test.

Chronic Thyroiditis in Man

As soon as the first histological sections of thyroid glands of animals immunized with extracts of their own thyroid glands were examined in our laboratory

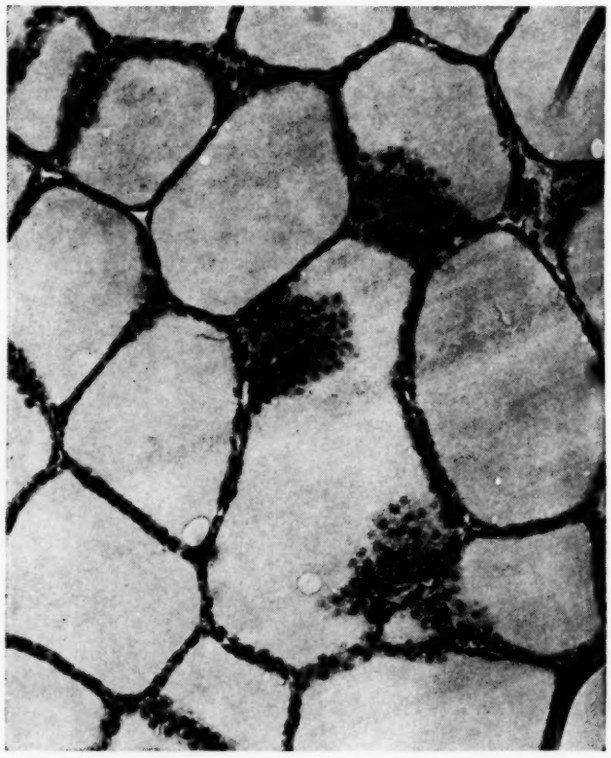

Fig. 3.—Photomicrograph of section of thyroid in rabbit 410, which was injected intradermally with 0.2 ml. of rabbit serum with Freund adjuvants on Jan. 4, 1955, showing normal pattern. Animal was killed on April 11, 1955.

in 1954, it became evident that the histological changes resembled in certain respects those seen in chronic thyroiditis in man. During the past two years we have had an opportunity to examine the serums of certain individuals suffering from various kinds of thyroid disease, including several patients in whom a diagnosis of chronic thyroiditis had been made either clinically or histologically. Of this latter group, 12 had circulating antibodies in various titers against human thyroid extract as demonstrated by the tanned-cell hemagglutination test. In none of the patients with other thyroid diseases was a thyroid antibody demonstrable. These findings in a typical experiment are shown in table 2.

Increasing serum dilutions (vol. 0.1 ml.) of (*a*) patient "Tre.," (*b*) patient "Tho.," (*c*) patient "May.," (*d*) patient "Bur.," (*e*) normal human serum (negative control), and (*f*) anti-human-thyroid rabbit serum 440 (positive control) were mixed with 0.1 ml. of human red blood cells of group O, previously tanned and coated either with a hundredfold diluted, heated human thyroid extract or with a two-hundredfold diluted normal human serum. As diluent, phosphate-buffered saline solution (pH 7.2) containing 0.5% normal rabbit serum was used. The tanning and coating of the red blood cells was done as described previously.[5] Tanned but uncoated cells were used as controls but were omitted from the table because they were negative. The tubes were kept at room temperature for two hours and then put in the refrigerator overnight. Several readings were taken during the observation period. The reading recorded in table 2 represents the pattern of sedimentation observed after standing overnight at 4 C.

TABLE 2.—*Reaction of Serums of Patients with Thyroiditis to Tanned Human Erythrocytes Coated with Human Thyroid Extract or Human Serum*

Dilutions of Patient's Serum or Rabbit Serum	Erythrocytes Coated with Human Thyroid Extract*					Erythrocytes Coated with Human Serum†
	Serum of Patients with Thyroiditis				Serum of Rabbit 440	Serum of Rabbit 440
	Tre.	Tho.	May.	Bur.		
1:5	++	+++	+++	+++	+++	+++
1:10	+++	+++	+++	+++	+++	++
1:20	+++	+++	+++	+++	+++	++
1:40	+++	+++	++	+	++	++
1:80	++	++	++	−	++	+
1:160	++	++	−	−	++	+
1:320	++	++	−	−	−	+
1:640	++	++	−	−	−	−
1:1,280	−	++	−	−	−	−
1:2,560	−	−	−	−	−	−

* Normal human serums gave negative reaction in all dilutions.
† Serums from all patients and normal human serum gave negative reactions in all dilutions.

As table 2 shows, the serums of four patients with thyroiditis were found to contain antibodies of various titers against human thyroid extract, as does the anti-human-thyroid rabbit serum used as the positive control. The normal human serum is negative. Furthermore, in contrast to the rabbit antiserum, the four patients' serums do not agglutinate cells coated with human serum.

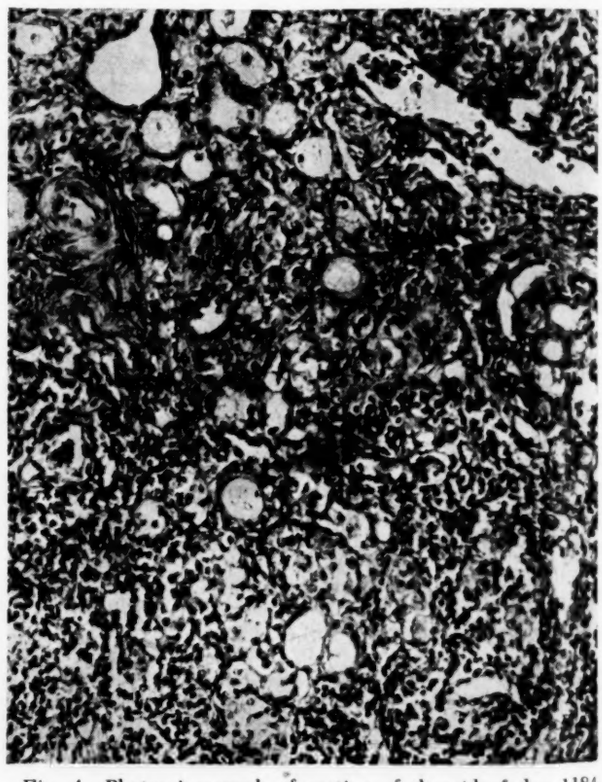

Fig. 4.—Photomicrograph of section of thyroid of dog 1184, showing one of more densely infiltrated areas, with slight degree of fibrosis evident, and cellular exudations into the lumens of some follicles.

The significant specificity of the results obtained was next tested in two ways. First, about 120 human serums submitted for routine serologic tests for syphilis from patients with various diseases were examined. None of these serums were positive. The experience gained by examination of a large number of control serums emphasized, however, the necessity of including as controls tanned, but uncoated cells in each experiment, since an occasional patient's serum caused agglutination of uncoated, tanned human cells, indicating the presence of an antibody of entirely different specificity directed against the human red blood cells themselves. The organ specificity of the antibody present in serums of patients with chronic thyroiditis was substantiated by an "inhibition-of-agglutination" test, as shown in the following experiment:

Increasing dilutions of (*a*) human thyroid extract, (*b*) human liver extract, (*c*) human spleen extract, (*d*) human kidney extract, (*e*) normal human serum, and (*f*) the extract of a colloid goiter from patient "Buc." were mixed with the serum of patient "Tho." (diluted 1:500). All extracts were prepared in exactly the same manner as the normal thyroid extract (50% w/v). After the mixtures were kept at room temperature for one hour, tanned cells coated with a hundredfold diluted, heated human thyroid extract were added. The resulting sedimentation pattern, as observed after the test tubes had stood overnight at 4 C, is recorded in table 3.

TABLE 3.—*Inhibition of Agglutination by Various Human-Organ Extracts*

Dilutions of Free Antigen	Human Organ Extracts		
	Thyroid	Liver*	Colloid Goiter
1:10	—	+++	—
1:20	—	+++	—
1:40	—	+++	—
1:80	—	+++	—
1:160	—	+++	—
1:320	—	+++	—
1:640	—	+++	—
1:1,280	—	+++	—
1:2,560	—	+++	—
1:5,120	+++	+++	—
1:10,240	+++	+++	+
Saline control	+++	+++	+++

* Extracts of spleen, kidney, and normal serum also gave +++ reactions in all dilutions and in saline control.

Occasionally, some difficulties were encountered in inhibition tests because of the lytic action of the liver and kidney extracts in higher concentrations. In this experiment, however, no lysis occurred. Only the extracts of normal and goiterous thyroid glands, and not those of other organs, inhibited agglutination. The goiter extract appears to inhibit in even higher dilutions than does the normal thyroid extract, possibly because of its greater colloid content. This experiment further proves the specificity of thyroid antibodies as they may occur in the serum of patients with chronic thyroiditis.

These antibodies are not of the cold agglutinin type, inasmuch as the hemagglutination reaction occurred at 37 C (98.6 F) as well as at room temperature. Of the four serums that gave positive hemagglutination reactions, one from patient "Tho." gave slight precipitation when mixed with thyroid extract and also revealed some evidence of complement-fixing activity. The three others were completely negative in both precipitation and complement fixation tests. The precipitation tests were carried out either in the conventional saline diluent or in an agar gel as described by Oudin.[10]

Report of Cases

The case histories of three typical patients in whose serums thyroid antibodies were detected (table 2) are as follows:

CASE 1.—A 35-year-old woman (Tho.) was treated at Buffalo General Hospital. In December, 1952, patient noticed a swelling in the region of the thyroid. By August, 1953, this swelling had increased, and there was moderate tenderness, slight dysphagia, and a drawing sensation. At the first hospitalization, Sept. 30 to Oct. 6, 1953, both lobes of the thyroid were enlarged, hard on palpation, and tender, with a smooth surface, but not fixed to the skin or surrounding structures. At surgical exposure, the left lobe of the thyroid was found to be grayish yellow in color, firm, and studded with nodules 3 to 10 mm. in size. One 10-mm. nodule was noted in the isthmus. The right lobe was somewhat smaller and of about the same color and consistency but without nodules. The entire gland was firmly adherent to the trachea.

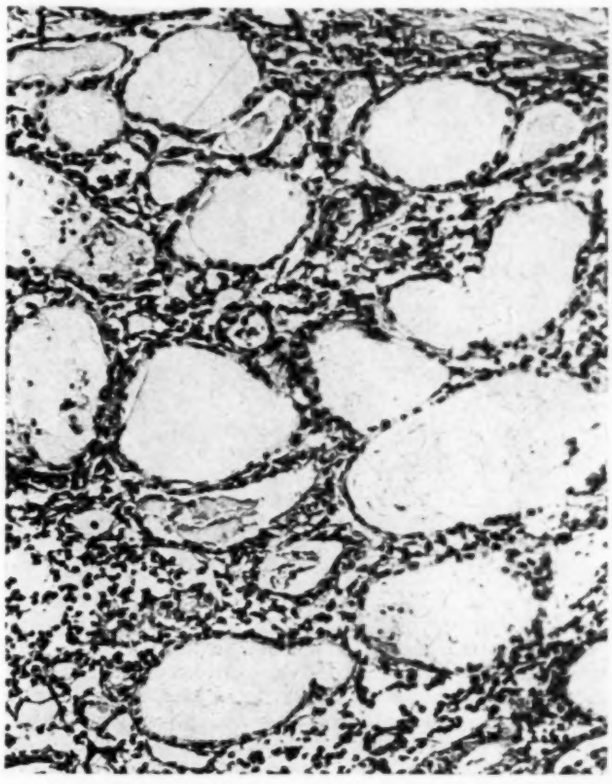

Fig. 3.—Photomicrograph of section of left lobe of thyroid removed from patient in case 1 in 1953, showing normal-sized acini, desquamated and exuded cells within the colloid, diffuse inflammatory infiltrations, and hyaline fibrosis.

A subtotal resection of the left lobe (weight 12 Gm.) and isthmus was performed. The outstanding histological finding was distinct infiltration by lymphocytes and plasma cells, obscuring the original acinar pattern. Thyroid follicles were small and contained little colloid. Desquamated epithelial cells intermingled with lymphocytes and leukocytes were present in their lumens. In several lobules, lymph follicles had formed including small thyroid acini in their center. The interlobular stroma was fibrosed and infiltrated by lymphocytes. Occasionally, giant-cell formation of the foreign body type around inspissated colloid could be observed. This entire process appears to be more advanced in some lobules than in others. In a few of them, it was in a relatively recent state, as numerous acini of normal size had not lost their colloid content and the infiltration by lymphocytes and plasma cells was of a more focal type. On the other hand, there were some atrophic lobules with hyalinization and

fibrosis of the interlobular stroma. Lymph follicles were present in some lobules, especially in the atrophic and diffusely infiltrated ones. These changes in their entirety can best be designated as chronic thyroiditis. Figure 5 shows some of the features described.

After this operation, the patient complained of a continued sensation of pressure in the region of the remaining right lobe of the thyroid. On the second hospitalization, Nov. 11-17, 1956, a hard and fairly movable mass, about 4 cm. in diameter, was

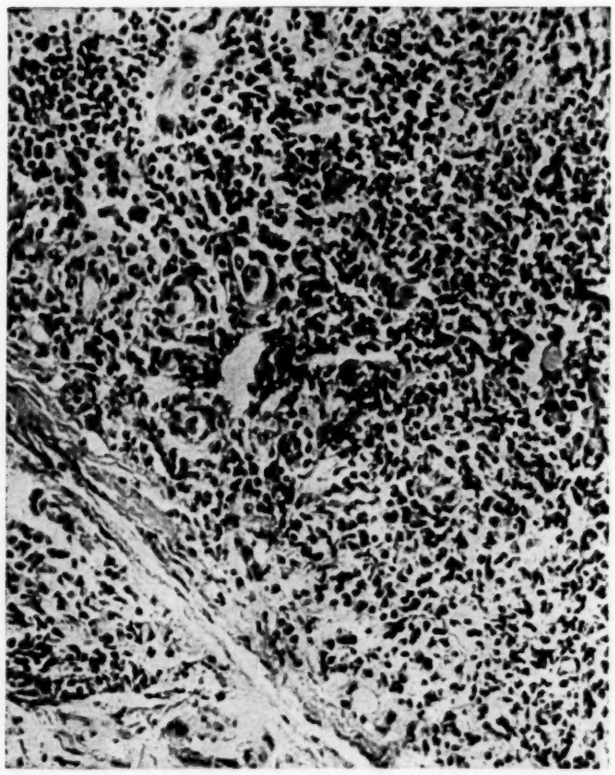

Fig. 6.—Photomicrograph of section of right lobe of thyroid removed from patient in case 1 in 1956, showing conspicuous diminution of normal colloid.

felt in the right lobe. The entire lobe was excised. It was firm, grayish tan, and nodular, measuring 6 by 4 by 2.5 cm.

Comparing the histological findings in the right lobe with those in the left, removed three years previously, the following differences could be noted: There was distinct fibrosis around several lobules. Some of them were small, appearing almost like diffuse lymphoid structures. The most prominent features were infiltrations by plasma cells in sheet-like arrangement. Only a few acini had remained with preserved epithelium and colloid. In numerous lobules, there were well-established lymph follicles, with prominent germinal centers or lymphocytic follicles surrounding a central pool of colloid-like fluid matter. Most of the acini contained only desquamated epithelium and numerous plasma cells or some inspissated colloid. Almost in every lobule some foreign body giant cells were seen surrounding eosinophilic material in some follicular lumens, with epithelial lining still preserved. The original follicular pattern, thus, was considerably disrupted. It was changed here and there into solid tubules or into small follicles with strongly eosinophilic epithelial cells. Some rare mitotic figures were seen in these enlarged epithelial cells of the solid area. All these findings were interpreted as severe changes of chronic thyroiditis, and the conspicuous diminution of normal colloid was the most outstanding feature (fig. 6).

Case 2.—A 38-year-old woman (Tre.) was treated at Buffalo General Hospital. This patient first noted an enlargement of her thyroid in 1953. Some "pills" and iodine taken for two months were without effect. In July, 1954, there was a gradual enlargement of the goiter associated with hoarseness, dysphagia, dyspnea, malaise and headaches. She was hospitalized from Sept. 27 to Oct. 5, 1954. Examination showed a bilateral enlargement of the thyroid, with the right lobe being larger than the left and somewhat tender. Signs of myxedema were noted.

Bilateral subtotal resection of the thyroid was carried out. The excised tissue was grayish white, stony hard, and slightly lobulated. There was constriction of the trachea and esophagus with firm adherence of the thyroid to these structures. The gland weighed 57 Gm. The right lobe measured 7 by 4 by 2.5 cm. and the left 5.5 by 3 by 2 cm.

On histological examination, the lobules appeared to be markedly constricted by bands of hyalinized collagenous tissue, extending into the remnants of the original follicles and blending with numerous plasma cells and lymphocytes. There were a few acini with pale staining, mostly solid tubules, and finely granular cytoplasm. These appeared to be almost obscured within the collagenous hyalinized tissue, replacing much of the original structure, and contained only rare remnants of pale-staining colloid within their narrow lumens. A few very small lymphocytic follicles are also seen. These findings were interpreted as indicating diffuse, chronic thyroiditis of the so-called Riedel's type (fig. 7).

Case 3.—A 44-year-old woman (Bur.) was treated at Lafayette General Hospital. In August, 1956, the patient experienced pain and swelling in the region of the right thyroid lobe for the first time. The pain radiated to the ear. In October, 1956, she noted similar symptoms on the left side. Physical examination revealed a hard nodular tumor mass in the region of the thyroid. She had had a 12-lb. (5 kg.) weight loss during the preceding two months. The basal metabolic rate was within normal limits. Roentgenographic studies showed a tumor mass just above the clavicle, displacing the trachea to the right. The

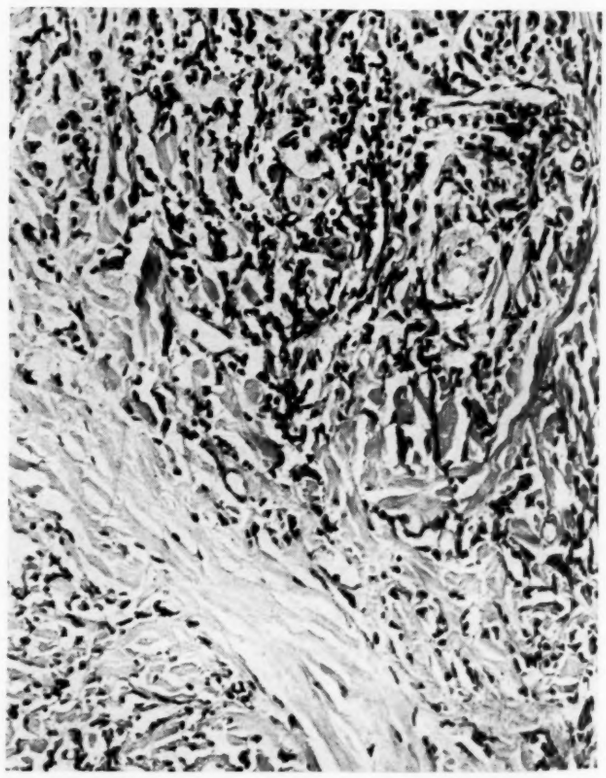

Fig. 7.—Photomicrograph of section of thyroid removed from patient in case 2.

clinical diagnosis was carcinoma of the thyroid. On Nov. 13, 1956, a total thyroidectomy was performed. The two lobes measured 5.5 by 4 by 2 cm. and 4 by 3 by 1.8 cm.

On histological examination, the lobules of the thyroid were found to be separated by hyaline fibrous bands. Some contained acini with considerable colloid and few "pseudo-tubercles." The infiltration by plasma cells and lymphocytes was marked. Other lobules consisted largely of tubercle-like granulomas, in the center of which was colloid, surrounded by palisading fibro-

blasts and numerous leukocytes. There were many giant cells of the foreign-body type around inspissated colloid. These granulomas had completely masked the original acinar pattern, and a few of them resemble small abscesses, due to the large number of leukocytes, particularly in areas where the colloid content had vanished. There were no lymph follicles and the fibrosing changes were very marked (fig. 8). The findings were interpreted as indicating chronic thyroiditis of the granulomatous (tubercle-like) type.

Since the pathogenetic mechanisms bringing about the various changes in the thyroid encountered in these three cases of the human disease are still under discussion, the merely descriptive term "chronic thyroiditis" appears as the most suitable. These changes represent a fundamental alteration in secretion and resorption of colloid, leading eventually to replacement of the original structure by granulomatous and fibrous tissue.

In six patients, changes of chronic thyroiditis were proved histologically, but no antibodies were found in their serums at the time of the present study. In three of them, the structural changes were extensive, marked, and fairly uniform. Of these, one patient underwent total thyroidectomy in 1952, and subtotal thyroidectomies were performed on the other two patients in 1954. In the other three, the picture of chronic thyroiditis was only moderately severe and there were fairly numerous follicles with normal-appearing colloid remaining.

Comment

Extracts of the thyroid gland can become antigenic within the same species or even within the same individual under certain experimental conditions. Rabbit thyroid extract elicited thyroid-antibody formation in rabbits, dog thyroid extract in dogs, and guinea pig thyroid extract in guinea pigs. These antiserums proved to be specific for thyroid extract. The question arises of whether these antibodies can be considered as true autoantibodies. The injection of rabbits that had been subjected to thyroidectomy with their own thyroid extract resulted in antibody formation, strongly supporting this hypothesis. Nevertheless, one could still maintain that during the preparation of the thyroid extracts certain alterations might have occurred in the immunochemical constitution of the thyroid extract. The autoantibody nature of the antibodies involved, however, seems established finally by the observation that the thyroid antibodies produced by immunization apparently react with and damage the thyroid glands of the antibody-producing animal itself. If an immunochemical change of the extract were responsible for its antigenic potency, then the change must have been minimal enough to allow the antibody to act on the antigen of the thyroid gland in situ. Therefore, we consider the phenomenon described to be an example of true autoantibody formation.

The serologic investigations of thyroid autoantibodies were considerably facilitated by the tanned-cell hemagglutination test recently introduced by Boyden. This test proved to be superior to the conventional complement fixation and precipitation tests by allowing the recognition of circulating antibodies in higher titers and in a considerable percentage of immunized animals in which the other tests were negative. Admittedly, considerable experience and watchfulness are necessary in the execution of the tanned-cell hemagglutination test, but, when carried out under exacting conditions, the test is most valuable not only because of its sensitivity but also because of its specificity.

Many problems still remain to be solved. For instance, an autoantibody of this type might disappear from the circulation sooner than other antibodies produced by active immunization because of the presence of its antigen counterpart within the body. Since the circulating antibody will be constantly absorbed by the tissue of the immunized animal itself, many difficulties will undoubtedly be encountered in the production of corresponding lesions by passively transferring immune serum into normal animals, as preliminary

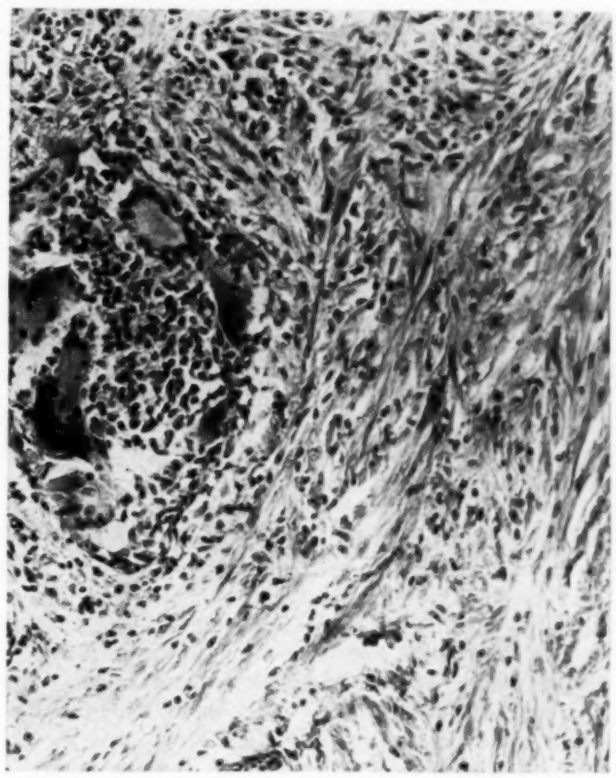

Fig. 8.—Photomicrograph of section of thyroid removed from patient in case 3.

experiments in our laboratory have already indicated. Furthermore, also, the possibility must be considered that antibodies other than those demonstrated in vitro are actually responsible for the disturbance in the thyroid gland. In this case, then, the circulating antibodies may be considered as a kind of indicator of the presence of incomplete or cell-bound types of antibodies. Similar considerations may apply in allergic encephalomyelitis of experimental animals.

The comparison of the histological pictures of experimental thyroiditis in animals with that of thyroiditis in man reveals certain similarities. One should not forget, however, that by immunization of experimental animals with thyroid extracts early stages of thyroiditis can be produced that one cannot expect to see in patients, who usually present an advanced stage of the disease. Circulating antibodies against extracts of human thyroid gland could be detected by the tanned-

cell hemagglutination test in some patients suffering from histologically proved chronic thyroiditis. Several serums examined electrophoretically have had normal or only slightly elevated gamma globulin values, and only a small proportion gave precipitation and an indication of complement fixation. Roitt, Doniach, Campbell, and Hudson,[11] in a recent preliminary communication, reported the demonstration of precipitating antibodies against human thyroid extracts in cases of thyroiditis of the Hashimoto type (lymphadenoid goiter). Significantly, all of their patients exhibited hypergammaglobulinemia. According to Roitt, Doniach, Campbell, and Hudson, the antigen involved is human thyroglobulin—paralleling our own experimental findings.

The human disease, chronic thyroiditis, might be due, therefore, to a similar mechanism of autoimmunization against constituents of the thyroid gland, specifically thyroglobulin, as is thyroiditis in artificially immunized animals. In the case of the animal experimentation, however, the thyroid extracts were incorporated in Freund adjuvants and injected parenterally in order to elicit antibody production. The role of the Freund adjuvants in the production of antibodies is considerable, though not fully understood. Their enhancing effects seem to result from the creation of a depot, as well as from the inflammatory response due to the presence of acid-fast bacilli. In preliminary experiments the use of Freund adjuvants without acid-fast bacilli also gave positive results, although the percentage of animals with demonstrable thyroid antibodies accompanied by thyroiditis was decreased in comparison to that in the control group that received the full Freund adjuvants.[12] One, therefore, might assume that in human chronic thyroiditis a slow but continuous release of thyroglobulin into the circulation acts as a constant antigenic stimulus, resembling the depot effect achieved in animal experiments by means of Freund adjuvants. Such an assumption is supported by demonstration of a free, thyroglobulin-like protein in the bloodstreams of patients suffering from thyroiditis, as reported recently by Owen and McConahey,[13] and Stemmermann.[14]

This concept of the pathogenesis of chronic thyroiditis does not explain the circumstances responsible for the excretion of thyroglobulin into the bloodstream. Under normal conditions, thyroglobulin presumably does not enter the circulation as an intact protein, being subjected to previous breakdown by the enzymes present in the thyroid gland.

As stated above, the pathogenesis of a number of human diseases has been attributed by some investigators to the effect of autoantibodies. The time seems to have come to establish certain criteria that ideally should be fulfilled in order to prove the role of an autoantibody in the pathogenesis of a particular disease, namely, (1) the direct demonstration of free, circulating antibodies that are active at body temperature or of cell-bound antibodies by indirect means; (2) the recognition of the specific antigen against which this antibody is directed; (3) the production of antibodies against the same antigen in experimental animals; (4) the appearance of pathological changes in the corresponding tissues of an actively sensitized experimental animal that are basically similar to those in the human disease. We believe that these requirements have come close to fulfillment in certain cases of human chronic thyroiditis. Nevertheless, what circumstances trigger the release of intact thyroglobulin into the bloodstream remains an unsolved problem.

Summary

Saline extracts of thyroid glands incorporated into Freund adjuvants were found to be antigenic not only for animals of the same species, such as rabbits, dogs, and guinea pigs, but even for the individual animal from which the thyroid extract was obtained. Purified rabbit thyroglobulin, when injected into rabbits, also proved to be antigenic. The tanned-cell hemagglutination test of Boyden provided a highly sensitive method for the demonstration of thyroid antibodies without any sacrifice of specificity. The autoantibody nature of this type of thyroid antibody was substantiated by the occurrence of marked histological disturbance in the thyroid glands of the immunized animals.

Human serums from patients with chronic thyroiditis were examined in the same way. Twelve patients were found whose serums contained circulating antibodies specifically directed against extracts of human thyroid glands. Again the tanned-cell hemagglutination test proved to be the most sensitive procedure, although occasionally antibodies could also be demonstrated by precipitation. The serologic and histological findings as they occur in certain cases of chronic thyroiditis in man appear to be comparable to those produced artificially in experimental animals. On the basis of these similarities, it is proposed that the pathogenesis of some types of chronic thyroiditis in man is related to autoimmunization against constituents of the patient's own thyroid gland, as is experimentally produced thyroiditis in animals, and that circulating thyroid antibodies may be the cause or may serve as the indicator of this process.

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CYCLIC ESTROGENIC HORMONE THERAPY OF ACNE VULGARIS

USE OF THE VAGINAL SMEAR TECHNIQUE IN EVALUATION AND TREATMENT

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• *Acne vulgaris was treated in a series of 21 female patients from 13 to 30 years of age by administering orally a preparation of conjugated estrogenic substances. The average daily dose was 3.9 mg., and the average duration of treatment was 8.9 months. The treatment was cyclical in that it was given only for the 14 days before the expected day of the menses. The results were good in seven patients and satisfactory in nine. A second series of 50 patients was then treated similarly, except that 8 of these received only a placebo and 12 received only the estrogen; 14 received estrogen for a time followed by a period of placebo medication, while 16 received the placebo for a time followed by a period of estrogen medication. None of the patients who received only the placebo showed results described as good; two had satisfactory results. The results were good in 24 and satisfactory in 13 of the 42 patients who received the estrogen. The effectiveness of the estrogen in influencing hormonal pattern was shown by making vaginal smears and determining the percentage of cornified cells in the smear; normal cornification denoted adequate physiological response and served as a guide in arriving at correct individual dosages. Patients who showed an initial estrogen deficiency by this criterion were found to require a significantly higher dosage. The results showed that estrogens administered during the postovulatory phase of the menstrual cycle are of value in the treatment of acne.*

An etiological relationship between hormones and acne is generally accepted. Estrogens, testosterone, progesterone, and pituitary gonadotropin have been given therapeutic trials with varying results.[1] This study was devised to determine the therapeutic efficacy of natural estrogens, administered by mouth in the postovulatory phase of the menstrual cycle, on female patients with acne. The vaginal smear technique of Dr. Ephraim Shorr was used to evaluate patients for initiation of therapy and to check on the response of patients to treatment with various doses of estrogens. The study covers two series of patients treated since 1942. The first is a pilot study and the second, a series using placebos for control.

Background

Although it is not known exactly how and why, there is good evidence that androgens aggravate and estrogens ameliorate acne. Many authors feel that the ratio of these two hormones is more important than the individual hormonal levels per se.

The following observations support the theory that androgens are a factor in the production of acne: 1. Acne is not seen in eunuchs or castrates and is seen rarely in prepubertal children.[2] 2. The incidence of acne is higher in males than in females.[2] 3. Masculinizing tumors and disorders of the pituitary and adrenal glands, such as arrhenoblastoma, adrenal cortical hyperfunction (Cushing's syndrome), and adrenal hyperplasia, are often accompanied by acne.[3] 4. Therapy with androgens sometimes produces acne. This is true even in the eunuchoid or castrate group and in prepubertal children.[3] Administration of adrenocorticotropic hormone or similar acting compounds which increase androgenic hormone levels has a similar effect.

The role of estrogens in the amelioration of acne is supported by the following observations: 1. Acne usually is less severe in the midportion of the menstrual cycle when estrogen levels are highest, and exacerbations occur premenstrually when estrogen levels decrease.[4] 2. In pregnancy, when the estrogen levels are high, acne is usually absent or much less severe.[4] 3. Assays for urinary estrogens have been reported as lower in female patients with acne than in controls.[5] 4. Treatment with estrogenic hormone substances has proved beneficial.[6]

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Outline of Study

Estrogenic hormones were administered during the postovulatory phase of the menstrual cycle, so that large doses could be given without suppressing ovulation or disturbing the menses.[7] With such administration most side-effects of estrogen administration are avoided, and there is no possibility of a cumulative effect.

Selection of Hormone.—Although parenterally administered estrogens are more predictable in regard to the physiological effect per unit dose, an oral medicament was chosen in order to eliminate the necessity of frequent clinic visits by the patients and thus insure that treatment was started on a particular day of the menstrual cycle in consecutive cycles. A preparation of conjugated estrogenic substances (Premarin) was selected because of its relative freedom from side-effects, such as nausea and vomiting, sometimes found with synthetic preparations.

Vaginal Smear Technique.—The vaginal smear technique[8] is a practical method of studying ovarian function and the physiological response to estrogenic hormone administration. The method is based on the estrogenic control of the proliferation of the vaginal epithelium. This proliferation causes a variation in the morphology and staining characteristics of the desquamated vaginal cells.

The technique was selected over other methods (urinary assays of estrogens, endometrial biopsies) because it is simple, inexpensive, and nontraumatic. The smear can be obtained, prepared, stained, and evaluated within a few minutes. The method permits continuous rather than episodic observation of ovarian function. This is of great value both in evaluating the individual patient as to type and degree of ovarian insufficiency and in planning the therapy. After the time of ovulation is determined, estrogens can be administered thereafter with no danger of disturbing the menstrual cycle.

The technique consists of the insertion of a pipet into the vagina, aspiration of a small amount of secretion containing exfoliated cells, transfer of this material to a glass slide, fixation, and staining. The Shorr modification of the Papanicolaou stain was used because it has the advantage of being a single differential stain. In performing a full-cycle series, a patient can take her own smears and store them in a bottle containing fixative until her next clinic visit.

The smear was used to determine the influence of estrogens on the vaginal epithelium. The patient took smears at home throughout one cycle. These smears were evaluated to determine the time of ovulation and the hormonal pattern. After the initiation of therapy, the response of the vaginal epithelium was followed by smears on the clinic visits.

The cornification index (percentage of cornified cells in the smear) was used to evaluate the therapeutic response. This index does not represent the total information gained from observation of the smear, since the effect of progesterone is not interpreted by it. But if used in the same patient at the same time of the cycle, it is indicative of the response to estrogens when compared with the cornification index of the pretreatment smear for the same time of the cycle.

This simplification would enable a physician with a minimum amount of training to evaluate and adjust the dosage in a patient previously evaluated by a competent endocrinologist. Use of this index also simplifies graphic representation.

The following conditions were considered as contraindications to estrogen therapy: (1) endometriosis, (2) evidence of persistent ovarian follicle, (3) cystic mastitis, (4) carcinoma of breast or female reproductive organs, (5) ovarian cyst, and (6) severe liver disease. None of our patients, however, was found to have these contraindications except one, who showed evidence of a persistent ovarian follicle on the vaginal smear series.

Pilot Study

The pilot study was carried out in the thyroid-endocrine clinic of the New York Hospital from 1942 to 1948 under the direction of Dr. Ephraim Shorr. The patients are not representative of the average patient with acne. They were referred for treatment because of evidence of ovarian insufficiency, menstrual irregularities, or failure of conventional methods to effect a cure of the disorder. Of over 50 patients studied, only 21 received estrogen therapy for a minimum period of three months and therefore warrant therapeutic evaluation.

In these 21 patients, the age varied from 13 to 30 years, with the average being 20.6 years. The average age of the patient at the onset of acne was 14 years. Nine patients had menstrual irregularity and eight had dysmenorrhea. Vaginal examination of 19 revealed 15 with apparently normal uteri and 4 with uteri classified as small for their age. The vaginal smear series was interpreted as being normal in 5, showing evidence of estrogenic hormone deficiency in 15, and being indeterminate in 2.

The preparation of conjugated estrogenic substances was administered orally for the 14 days before the expected date of the menses. The usual starting dose was 1.25 mg. daily. With each succeeding cycle the dose was raised 1.25 mg. daily until a good clinical result was obtained or the vaginal smear showed adequate physiological response (normal cornification). Dosage was then decreased by 1.25 mg. daily in succeeding cycles as long as improvement held. Maintenance dosage consisted of the minimal amount of hormone which sustained improvement.

Therapeutic results in this series of 21 patients were based on clinical judgment and serial photographs. The length of treatment ranged from 3 to 28 months, with the average time being 8.9 months. The maximum daily dosage of conjugated estrogenic substances ranged from 1.25 to 8.75 mg., with the average being 3.9 mg. The results were good in seven patients, or 33.3%; satisfactory in nine, or 42.8%; and unsatisfactory in five, or 23.8%. In two patients there was the side-effect of premenstrual breast tenderness and in one, increased dysmenorrhea.

Second Series

The second series of patients was observed in the dermatology clinic of the New York Hospital from 1948 to 1953. It is representative of the average female patient with acne, as unselected patients ad-

mitted to the clinic were referred for study. Selection for inclusion in the series was on the basis of willingness to cooperate and availability for follow-up studies. All patients who completed studies and one course of hormone or placebo therapy are included in the statistics.

Twelve patients received only estrogens, and eight, including the patient with the persistent ovarian follicle, received only placebo. Thirty received both estrogens and placebo, 16 receiving the placebo before the estrogens and 14 after the estrogens. In all, 42 patients were treated with estrogens. The ages of the 50 patients in the series ranged from 11 to 30 years, with the average being 14.1 years. Menstrual irregularity, dysmenorrhea, and premenstrual exacerbation of acne were present in 30.4%, 60%, and 78%, respectively, of the group. Adult breast development was present in 46%, while adolescent development was present in 54%. Basal temperature studies were carried out on 13 patients. Nine were interpreted as ovulatory and four as anovulatory.

The initial vaginal smear studies were interpreted as being indicative of apparently normal ovarian function in 14 patients, or 28%; evidence of estrogen deficiency in 27, or 54%; indeterminate in 8, or 16%; and persistent follicle in one, or 2%.

This series was a controlled study in that courses of hormonal and placebo therapy were alternated without the knowledge of the patient. Weak lotio alba (4% active ingredients) was used by all patients. Pustule counts at the same phase of successive cycles were used as a criterion for evaluating therapeutic response. The estrogen preparation or the placebo was administered in the same manner as described in the pilot study.

Results of the estrogen therapy in the 42 patients were good (75 to 100% improvement) in 24, or 57%; satisfactory (50 to 75% improvement) in 13, or 31%; and unsatisfactory (less than 50% improvement) in 5, or 12%. Length of the treatment averaged 6.8 months, with a range of 3 to 18 months. Maximum daily dosage averaged 6 mg., with a range of 1.25 to 12.5 mg. (see figure).

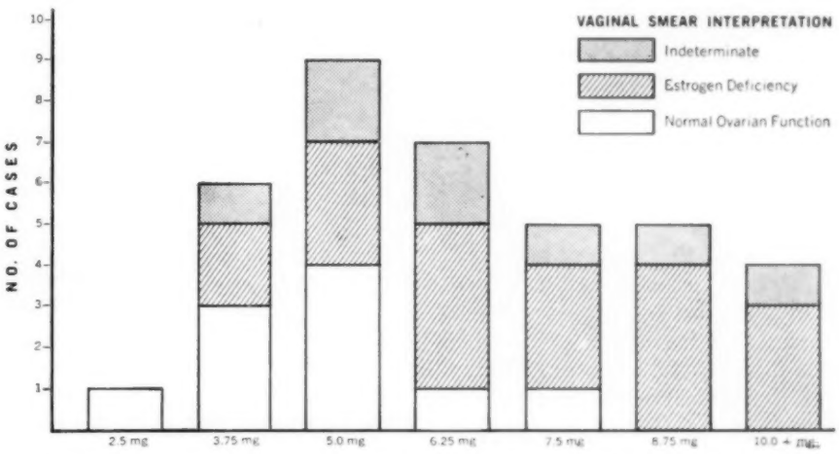
Of the 8 patients who received only placebo and the 16 who received placebo before estrogens, none showed good results. Two, or 8%, had satisfactory (50 to 75% improvement) results and 22, or 92%, unsatisfactory (less than 50% improvement). Of the 14 patients who received placebo after estrogens, 3, or 22%, held the improvement they attained and 11, or 78%, had a relapse. Length of treatment average 4.5 months, with a range of 2 to 18 months.

In correlating the maximum dosage of estrogens with the findings on vaginal smear in successfully treated patients (those showing more than 50% improvement), it is seen that those patients with evidence of estrogenic hormone deficiency required on the average higher doses than those with apparently normal ovarian function. No patient with normal ovarian function received more than 7.5 mg. of conjugated estrogenic substances daily, while seven patients with estrogen deficiency received doses higher than this amount.

Surprisingly few side-effects were encountered. Three patients receiving hormones complained of premenstrual breast tenderness, which, however, was not severe enough to necessitate stopping therapy. Symptoms were ameliorated when a lower dosage was given. Two patients on hormone therapy and one on placebo reported delayed menses. One patient on each type of therapy reported increased dysmenorrhea. One patient receiving hormones reported increased and prolonged menstrual flow.

Summary

Our results indicate that the administration of estrogens in the postovulatory phase of the menstrual cycle is of value in the treatment of acne. The optimum dosage varies considerably and has to be individualized for each patient. Those patients interpreted as showing estrogen deficiency in the vaginal smear series required on the average a significantly larger amount of hormones than those interpreted as having normal ovarian function.



Correlation of maximum dosage of conjugated estrogenic substances (Premarin), administered daily in the postovulatory phase of the menstrual cycle, with vaginal smear series interpretation in the 37 successfully treated (more than 50% improvement) cases in the second series.

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The Shorr modification of the Papanicolaou stain is available on request from Ayerst Laboratories, Inc., New York.

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ACQUIRED ARTERIOVENOUS FISTULA WITH BACTERIAL ENDARTERITIS AND ENDOCARDITIS

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and
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• *The problem of endarteritis and endocarditis complicating acquired arteriovenous fistula was encountered in two patients. Each patient was hospitalized because of a febrile illness and was found to have a large arteriovenous communication related to prior gunshot wound. The first patient was shown to have endarteritis in a fistula measuring 1 cm. in diameter between the femoral artery and vein, and endocarditis was considered to be present because of aortic insufficiency and peripheral embolic phenomena. His temperature remained elevated despite therapy with penicillin and streptomycin but promptly became normal after surgical removal of the fistula. The second patient, with an extensively calcified aneurysm involving the subclavian vessels, was not conclusively proved to have endarteritis. His temperature also showed no change during penicillin and streptomycin therapy but returned to normal after excision of the fistula. The first patient died one year after surgery, with manifestations of severe aortic insufficiency, and the second made a good recovery. These cases illustrate that in certain instances removal of an arteriovenous fistula may contribute greatly to the control of complicating intravascular infection by antimicrobial drugs.*

The recognition of bacterial endarteritis in acquired arteriovenous aneurysms is uncommon. Only 13 patients with this complication have been described in the American literature.[1] Five of these patients had bacterial endocarditis in addition to endarteritis.[2] Endocarditis in the absence of endarteritis has not been reported as a complication of arteriovenous fistula in man.

Recently, two cases of acquired arteriovenous fistula have been encountered in which the problem of endarteritis and endocarditis has arisen. After surgical removal of the fistula, combined with antibiotic therapy, both patients improved rapidly. These patients are the subject of the present report.

Report of Cases

Case 1.—A 34-year-old male was admitted to Grady Memorial Hospital on Oct. 19, 1954. For seven weeks he had experienced increasing shortness of breath and edema of the scrotum and lower extremities. Five weeks before hospitalization his temperature had been 100.2 F (38 C) orally and his blood pressure 140/80 mm. Hg. At that time, moist inspiratory rales were audible at the lung bases posteriorly. The heart was enlarged to the anterior axillary line. A harsh grade 2 systolic murmur was audible at the apex, and a grade 1 high-pitched diastolic murmur could be heard at the left sternal border. There was pitting edema of the scrotum and lower extremities. Moderate improvement in the symptoms of heart failure followed digitalization and administration of a mercurial diuretic. Three weeks before admission, pleuritic pain appeared on the left and shortness of breath became more marked. The patient's temperature was 102 F (39 C). Procaine penicillin G, 600,000 units daily, was administered intramuscularly for six days. Sulfadiazine was also prescribed, but the amount actually taken is unknown. Shortly before admission, chest pain on the left became more intense and was associated with hemoptysis and increasing dyspnea.

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History.—According to the patient's history, he had been shot in the left thigh with a .32-caliber pistol in 1942. The bullet penetrated the thigh to the opposite cutaneous surface and was palpable under the skin. Without medical aid, the patient removed the bullet by picking it out with a pocket knife. In 1948, a stab wound into the first intercostal space on the left anteriorly produced a pneumothorax. Examination of the heart revealed no abnormalities, and the blood pressure was 120/70 mm. Hg. The extremities were described as normal, and peripheral pulses were present. The Kahn test was negative. Recovery was prompt and complete.

In 1952, the patient received another gunshot wound in the lower part of the left thigh with a .38-caliber pistol, the bullet passing completely through the soft tissues. Dorsalis pedis pulses

were palpable, and a roentgenogram of the lower part of the femur showed no abnormalities. Penicillin was given for four days, and the wound healed rapidly without apparent complication.

For several years before admission the patient had experienced a buzzing sensation in the left thigh. For two years he had noticed swelling of the left leg and thigh following long periods of standing. Several months prior to the present admission the patient had had a tooth extracted. There was no history of venereal disease other than gonorrhea in 1937. No history of rheumatic fever or chorea was obtained.

Physical examination.—Physical examination revealed a temperature of 97.8 F (36 C); pulse rate of 88; respiratory rate of 32 per minute; and blood pressure in the left arm of 130/40 mm. Hg, in the right arm of 140/46 mm. Hg, and in the right leg of 240/70 mm. Hg. Blood pressure could not be obtained in the left leg. There were marked orthopnea and dyspnea. Many cutaneous scars were present, especially on the extremities. No clubbing of the digits or cyanosis was noted. Multiple dark-red splinter hemorrhages were observed under the nails of the left thumb and right great toe. The pupils reacted to light and in accommodation. Two small hemorrhages were observed in the left ocular fundus. Purulent material was present in the socket of an upper premolar tooth. Moist inspiratory rales were heard throughout both lungs. Systolic and diastolic thrills were palpable at the base of the heart. The border of cardiac dulness on the left extended to the midaxillary line in the sixth intercostal space. Grade 4 systolic and diastolic murmurs were heard in the primary and secondary aortic areas, and a grade 3 systolic murmur and a rumbling diastolic murmur were audible at the

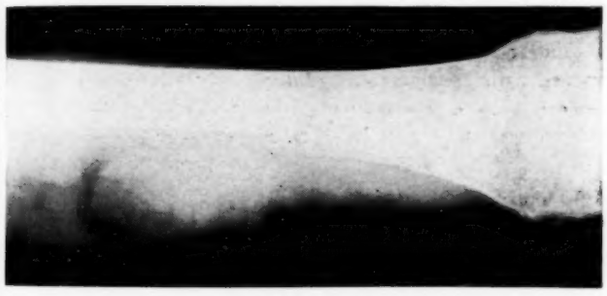

Fig. 1.—Roentgenogram of left thigh, showing arteriovenous aneurysm of femoral vessels (case 1).

apex. The liver was enlarged 4 fingerbreadths below the costal margin, but the spleen was not palpable. There was edema of the feet and legs, most marked on the left. The superficial veins of the left leg and thigh were dilated and prominent. A pulsating mass measuring 8 by 5 cm. was present in the lower left part of the thigh in the region of the femoral vessels. A continuous thrill was palpable in this area, corresponding to a loud continuous murmur with systolic accentuation. Pistol-shot sounds were heard over the femoral arteries in both legs. Dorsalis pedis and posterior tibial pulsations were absent on the left.

Initial Laboratory Data.—The serologic test for syphilis was negative and the urinalysis normal. Blood hemoglobin concentration was 9.4 Gm. per 100 cc. and the hematocrit 36%. Leukocyte count was 6,750 per cubic millimeter, with 2% basophils, 8% stab forms, 41% segmented neutrophils, 43% lymphocytes, and 6% monocytes. An adequate number of platelets were seen on smear. The blood urea nitrogen level was 33 mg. per 100 cc. Arm-to-tongue circulation time was 17 seconds; antecubital venous pressure was 164 mm. of saline solution. A roentgenogram of the left thigh (fig. 1) showed an oval soft tissue mass at the medial aspect of the femur. Calcification was noted in the inferior portion of the mass. An electrocardiogram was interpreted as showing left ventricular hypertrophy.

Course.—Initial therapy consisted of bed rest, a diet limited to 200 mg. of sodium, redigitalization, and mercurial diuretics. During the first four hospital days, chest pain subsided, dyspnea lessened, pulmonary rales cleared, and a weight loss of 10 lb. (4.5 kg.) was recorded. Fourteen of 16 blood cultures obtained during the initial four hospital days grew Micrococcus pyogenes var. albus which was hemolytic but coagulase-negative and mannitol-negative. Four cultures also revealed a microaerophilic diphtheroid. On the fourth hospital day, antibiotic therapy of 12 million units of penicillin (1 million units intramuscularly every 2 hours) and 2 Gm. of streptomycin (1 Gm. intramuscularly every 12 hours) daily was started. Although symptoms of congestive heart failure had disappeared, a chest roentgenogram on the 10th hospital day (fig. 2) showed no change in cardiac size or degree of pulmonary congestion as compared to earlier films. Temperature continued to reach levels of 100 to 101 F (37.8 to 38.3 C) daily. Because of pain at the sites of intramuscular in-

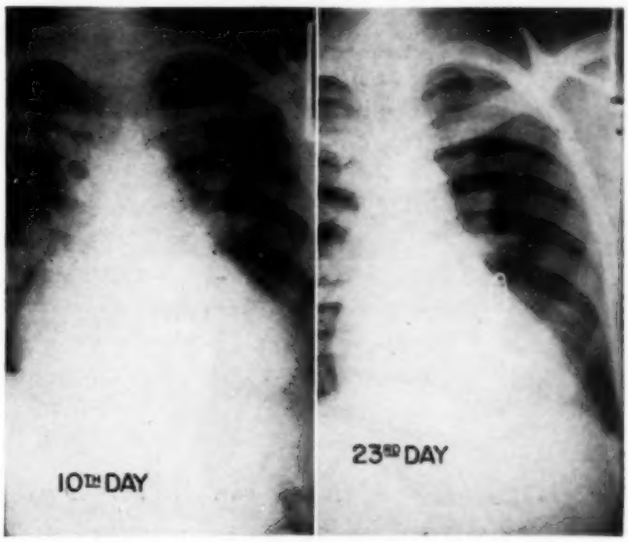

Fig. 2.—Chest roentgenograms before and after removal of femoral arteriovenous aneurysm (case 1).

jection, penicillin was given by slow intravenous infusion (6 million units in 1,000 cc. of 5% dextrose in water over a period of 6 to 10 hours twice daily) beginning on the 10th hospital day (fig. 3).

On the 11th hospital day the left femoral arteriovenous fistula was removed with the patient under general anesthesia. A longitudinal incision was made in the medial aspect of the lower part of the left thigh, and the adductor canal was entered. A saccular dilatation of the femoral artery, measuring 8 by 5 cm., was encountered protruding medially. In this area a communication was present between the femoral artery and vein. Both vessels were dissected free above and below the aneurysm. The proximal artery, distal artery, distal vein, and proximal vein were ligated and divided in that order, and the arteriovenous aneurysm was removed.

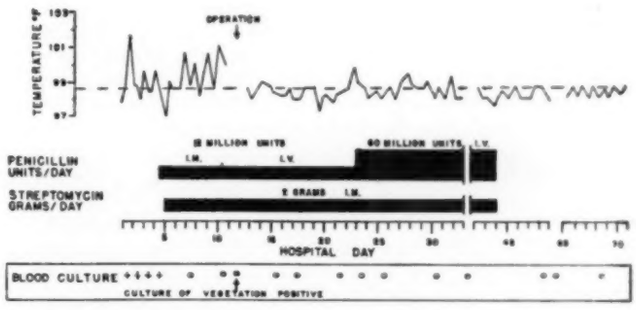

Fig. 3.—Hospital course in patient in case 1.

In the surgical specimen (fig. 4) a communication 1 cm. in diameter was present between the femoral artery and vein. A number of vegetations was located within the aneurysm near the opening of the distal artery. Microscopically, deposits of calcium and colonies of bacteria were visible in the vegetations (fig. 5). Several vegetations were removed with aseptic technique, crushed, and placed in tryptose phosphate broth. M. pyogenes var. albus grew in these cultures, and this organism was shown to have the same biochemical characteristics as the Micrococcus obtained from the blood. Antibiotic sensitivity stud-

ies performed on both organisms revealed inhibition by 10 mcg. of chlortetracycline, tetracycline, and chloramphenicol per cc. and resistance to 10 units of penicillin per cubic centimeter. The Micrococcus isolated from the vegetations was also found to be resistant to 100 mcg. of streptomycin per cubic centimeter.

The patient improved rapidly and became ambulatory. During the early postoperative period the temperature became normal. The only changes in the cardiac findings were a slight decrease in the systolic thrill and murmur at the base and a decrease in heart size on roentgenogram (fig. 2). Blood pressure

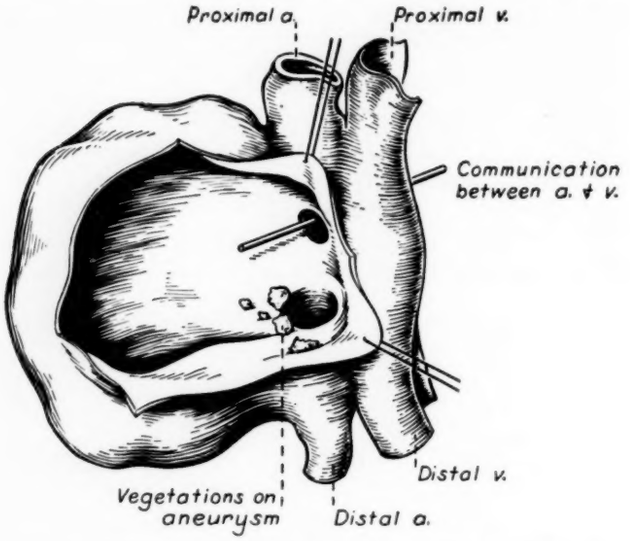

Fig. 4.—Arteriovenous aneurysm, drawn from surgical specimen (case 1).

remained at the previous level of 140/40 mm. Hg. Numerous blood cultures containing penicillinase taken during the postoperative period were sterile. On the 22nd hospital day the patient experienced the sudden onset of anterior chest pain and severe frontal headache. The right knee jerk was absent, but no other changes from previous examinations were noted. An electrocardiogram revealed no changes of significance. Lumbar puncture revealed an initial spinal fluid pressure of 110 mm.; the fluid was cloudy and contained 8 erythrocytes and 1,590 leukocytes per cubic millimeter, with lymphocytes predominating. The cerebrospinal fluid was sterile on culture and had normal concentrations of protein, sugar, and chloride. Another specimen of cerebrospinal fluid obtained approximately 12 hours later contained no erythrocytes and 632 leukocytes, 90% of which were lymphocytes. Penicillin dosage was increased from 12 million to 60 million units daily (30 million units in 1,000 cc. of 5% dextrose in water given intravenously over a period of 6 to 10 hours twice daily). The patient's temperature rose to 99.8 F (38 C) at the onset of this episode, but blood cultures were negative. Headache subsided in 48 hours, and the right knee jerk returned to normal.

Administration of penicillin and streptomycin was discontinued on the 44th hospital day, after 41 days of continuous therapy. On the 48th hospital day the patient complained of dizziness, which persisted for the remainder of the hospital stay. No additional complications developed. The patient was discharged on the 71st hospital day.

Congestive heart failure developed within one month after discharge, and the patient was hospitalized because of this complication in March, May, and October, 1955. On all occasions the findings were those of marked congestive heart failure caused by aortic insufficiency. There was no evidence of infection, and numerous blood cultures were sterile. On Nov. 6, 1955, the patient died suddenly at home. Prior to the time of death, manifestations of congestive heart failure were minimal. Permission for autopsy was not granted.

This patient was proved to have endarteritis in an arteriovenous aneurysm involving the femoral artery and vein. Bacterial endocarditis was also thought to be present, as evidenced by aortic insufficiency and peripheral embolic phenomena. Bacteriological cure was achieved, although the patient continued to show manifestations of severe aortic insufficiency. It seems likely that death was a consequence of severe damage to the aortic valve produced by bacterial endocarditis one year previously.

Case 2.—A 33-year-old male sustained a bullet wound in the left midsubclavicular region in January, 1951. The left radial pulse was barely palpable and hemopneumothorax was present on the left. On the 12th hospital day, a loud machinery-like murmur was heard over the left anterior part of the chest, and a thrill was palpable in this area. Blood pressure in the right arm was 150/60 mm. Hg and in the left, 115 mm. Hg systolic; a satisfactory diastolic pressure could not be obtained in the left arm. A diagnosis of traumatic arteriovenous fistula involving the left subclavian artery was made. The patient was discharged from the hospital after 26 days and was to be followed as an outpatient until sufficient collateral circulation developed to permit corrective surgery. When discharged he was asymptomatic and there was no roentgenographic evidence of cardiomegaly.

The patient was readmitted three months later for consideration of corrective surgery. He was asymptomatic and had been performing hard physical labor without difficulty. His blood pressure was 150/90 mm. Hg on the right and 140/80 mm. Hg on the left. His pulse was regular. The murmur and thrill were unchanged. The left arm was considerably larger than the right but was warm and functioned well; the left radial pulse was weakly palpable. Cardiovascular studies revealed slowing of the pulse on manual compression of the subclavian artery, rapid circulation time, increased stroke volume, decreased peripheral resistance, and increased blood volume. A chest roentgenogram revealed cardiomegaly and pulmonary congestion. Surgery was recommended but was refused.

The patient was lost to further follow-up for over three years, until Oct. 30, 1955, when he returned complaining of dyspnea, pleuritic chest pain, fever, chills, and productive cough of four days' duration. On admission the temperature was 103 F (39 C); the pulse rate was 144 and irregular due to auricular fibrillation. The blood pressure in the right arm was 170/100 mm. Hg and in the left, 165/100 mm. Hg. The murmur and thrill associated with the arteriovenous fistula were unchanged. The left arm was much larger than the right and showed extensive collateral circulation about the shoulder. The heart was enlarged, but no cardiac murmurs were heard, even after manual

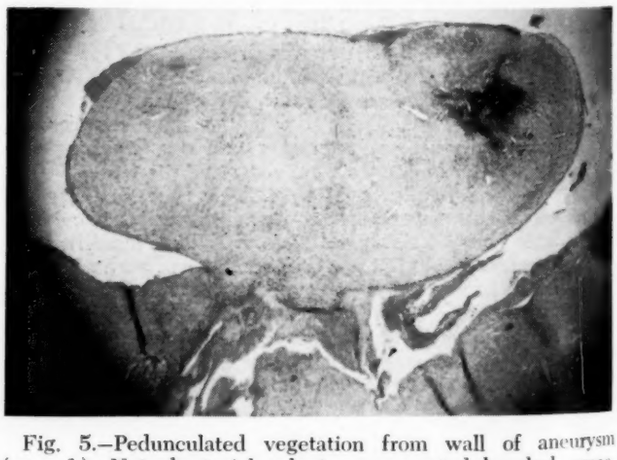

Fig. 5.—Pedunculated vegetation from wall of aneurysm (case 1). Note bacterial colonies represented by dark areas.

compression of the fistula. Moist rales were heard at the lung bases. A chest roentgenogram revealed marked cardiomegaly and considerable congestion or infiltration in both midlung fields. A well-defined irregular calcified mass with ring-like formations was noted in the region of the aneurysm. Several metallic foreign-body fragments were also present (fig. 6). The electrocardiogram showed auricular fibrillation and changes suggestive of right ventricular hypertrophy. The blood leukocyte

count was 11,560 per cubic millimeter, with a normal differential; hemoglobin concentration was 11.8 Gm. per 100 cc. Urinalysis revealed a 3+ reaction for protein, but the specimen was normal on microscopic examination; blood urea nitrogen concentration was 8 mg. per 100 cc. Venous pressure in the right arm was 170 mm. of saline solution and in the left, 480 mm. The arm-to-tongue circulation time was 20 seconds bilaterally. During the first two days, five blood specimens cultured aerobically and anaerobically were sterile. A few colonies of pneumococci grew on sputum culture.

On the second hospital day (fig. 7), the patient was started on therapy with aqueous penicillin, 1 million units every two hours, and streptomycin, 0.5 Gm. twice daily. He was also digitalized and his sodium intake was restricted. Two days after admission, he was observed by a nurse to have a generalized seizure. No neurological residuals were noted, and examination of the cerebrospinal fluid was negative. The symptoms of dyspnea and cough improved, but, in spite of antibiotic therapy, he remained febrile. On the 18th day, the dosage of penicillin was increased to 24 million units intravenously per day.

The arteriovenous aneurysm was removed on the 19th hospital day. A large calcified mass surrounded the area of the fistula, making removal extremely difficult. An arteriovenous communication was encountered between the third portion of the subclavian artery and vein. A large calcified false aneurysm encased the fistula, and numerous vascular channels existed between the fistula and the false aneurysm. The fistula and much of the calcified shell were removed. An area of the endothelial surface of the excised fistula had an irregular trabeculated appearance. M. pyogenes var. albus which was coagulase-negative grew in a culture of a homogenized portion

Fig. 6.—Roentgenogram of left shoulder, showing extensive calcification and metallic fragments at site of arteriovenous aneurysm (case 2).

of this tissue. Careful microscopic examination of selected areas of the fistula, however, revealed no evidence of an inflammatory process.

The postoperative course was uneventful except for elevated temperature that persisted for five days. Because of the possibility that this represented a drug fever, use of penicillin was discontinued and chlortetracycline, 1 Gm. per day, was substituted. No significant elevation of temperature occurred after chlortetracycline therapy was started. On the 13th postoperative day, administration of all antibiotics was stopped. An unsuccessful attempt was made to produce fever by administration of 48 million units of penicillin in two days.

When the patient was discharged on the 26th postoperative day, his condition was improved, although the heart had not decreased in size. The left arm remained warm and functioned well. Venous pressure on the right was 80 mm. of saline solution, and the arm-to-tongue circulation time was 10 seconds. Auricular fibrillation continued. After chemotherapy was stopped, blood cultures were consistently negative.

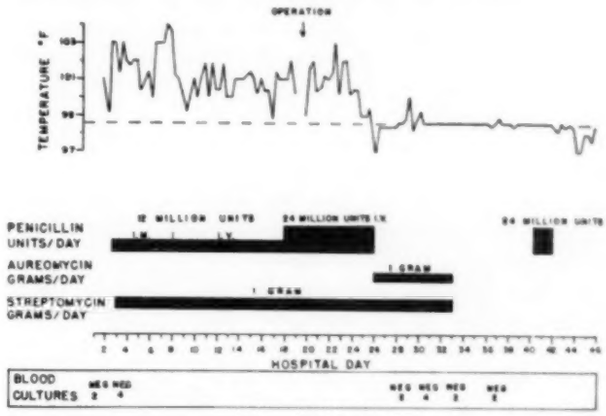

Fig. 7.—Hospital course in patient in case 2.

One month later the patient was readmitted for attempted conversion of the auricular fibrillation. He had been asymptomatic in this interval and had continued taking digitalis, 0.1 Gm. per day. He was afebrile and appeared well. The blood pressure was 140/100 mm. Hg in the right arm and unobtainable in the left arm. No murmur or thrill was detected at the former site of the arteriovenous fistula. The auricular fibrillation was converted to normal sinus rhythm with quinidine, and the heart subsequently decreased significantly in size.

This patient was not conclusively proved to have endarteritis in his arteriovenous fistula. However, the prompt defervescence after surgical excision of the fistula suggests this diagnosis. Although the Micrococcus cultured from the surgical specimen cannot be disregarded, this micro-organism was not necessarily the etiological agent. The occurrence of extensive calcification at the site of the aneurysm added greatly to the difficulties in surgical removal and in subsequent pathological study.

Comment

These cases are similar in many respects to those reported by others.[1] In all previous instances, arteriovenous communications which were the site of endarteritis have been large and have involved iliac, femoral, or subclavian vessels. Most of the fistulas had been present for many years before the development of endarteritis or endocarditis, but this interval ranged from a few months to 53 years. Although the majority of the fistulas were related to gunshot wounds, only two were incurred in military service.[3]

The clinical manifestations of endarteritis alone are similar to those of bacterial endocarditis, except that peripheral embolic phenomena are absent in the former. The nail bed and retinal hemorrhages and aortic insufficiency in case 1 strongly indicate that endocarditis was present in addition to endarteritis. In all reported cases of endocarditis complicating endarteritis, the aortic valve has been involved. In the patient reported by Parmley and others,[1a] vegetations were also present on the mitral valve.

The repeated finding of M. pyogenes var. albus in case 1 is unique. In previous reports of bacterial endarteritis in arteriovenous fistulas, the infecting organism has been Streptococcus viridans in every case except two; in one [1e] Str. faecalis was isolated, and in another [11] a "hemolytic Streptococcus" was the etiological agent.

The experimental work of Lillehei and co-workers [4] has contributed to an understanding of the mechanisms involved when endocarditis complicates arteriovenous fistula. These investigators produced bacterial endocarditis and, in some instances, endarteritis in dogs by construction of large arteriovenous fistulas. If fistulas were of sufficient size and duration, endocarditis developed spontaneously, but this complication could be hastened by the injection of bacteria. In these animals combined antibiotic and surgical therapy proved relatively ineffective.[5]

Surgical excision and antimicrobial therapy have effected a cure in all reported cases of endarteritis without endocarditis, except two that were cured by surgery alone.[6] Recently the tendency has been to attempt to control the infection with antibotics prior to surgical removal. In two reported cases, control of infection was not possible with antibiotics alone, and defervescence occurred only after the infected arteriovenous aneurysm was removed.[7] Case 1 demonstrated this point most clearly. There have been no cures reported in patients who also had endocarditis, regardless of the type of therapy, although the patient treated by Heckler and Tikellis [1d] had not shown evidence of infection for 29 days postoperatively when she died of a pulmonary embolus.

It is of interest that, in the patient described by Kahn,[1m] numerous cultures of blood drawn from antecubital veins were negative, and it was not until blood cultures were obtained from the femoral vein proximal to the fistula that the infecting organism was identified. This technique was not employed in case 2, but, in retrospect, it might have proved helpful.

Summary

Bacterial endarteritis and endocarditis occasionally develop in patients with acquired arteriovenous aneurysms. Endarteritis usually occurs in large fistulas of long standing and is most often caused by Streptococcus viridans. In all reported cases of endocarditis complicating endarteritis, the aortic value has been involved and the outcome has been fatal. One of the patients described in this report had a large arteriovenous aneurysm with bacterial endarteritis and endocarditis caused by Micrococcus pyogenes var. albus. Bacteriological cure was achieved, but the patient died one year later of the consequences of severe damage to the aortic valve. Surgical removal of the infected fistula appeared to contribute greatly to the control of the infection.

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Drs. Robert Hausman and Charles LeMaistre helped in the preparation of this paper.

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2. Footnote 1*a* through *e*.

3. Footnote 1*e* and *i*.

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6. Footnote 1*f* and *h*.

7. Footnote 1*d* and *k*.

Tranquilizing Drugs.—The use of [tranquilizing] drugs rests on the premise that psychiatry deals with "mental illness" and that such illness presents a problem essentially analogous to that encountered in medicine (and particularly in infectious disease). There is evidence to suggest that this "medical" model of behavioral disturbance is inadequate and misleading. If such disturbances do not constitute "diseases" which manifest themselves in certain "signs" and "symptoms," then measures based on this concept are likely to be faulty and probably harmful to patient, physician, or society.—T. S. Szasz, M.D., Some Observations on the Use of Tranquilizing Drugs, *A. M. A. Archives of Neurology and Psychiatry*, January, 1957.

NEUROLOGICAL MANIFESTATIONS AFTER ANTIHYPERTENSIVE THERAPY WITH MECAMYLAMINE

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• *Severe neurological manifestations including depression, agitation, euphoria, hallucinations, hyperreflexia, and especially a coarse, flapping tremor were seen in eight patients who had been receiving mecamylamine and hydralazine for the treatment of malignant hypertension. Analysis of the circumstances make it unlikely that the existing azotemia, the administered hydralazine, or possible vascular disease of the brain could be the causes of this syndrome. The mecamylamine was given in doses ranging from 48 mg. orally to 430 mg. parenterally per day. In one patient the existing chronic glomerulonephritis progressed to a fatal anuria, and in one other a widespread arteriosclerosis and advanced arteriolar nephrosclerosis terminated in hyperpyrexia and coma. In the six patients who survived, however, withdrawal of the mecamylamine was followed by disappearance of the symptoms within two weeks.*

In hypertensive patients it is usually possible to produce autonomic blockade and lowered blood pressure with quaternary ammonium compounds, such as hexamethonium and pentolinium salts. Except for fibrinous pneumonitis, which has become vanishingly rare,[1] most toxicity is directly attributable to autonomic blockade and includes excessive hypotension, paralytic ileus, and urinary retention as well as annoying but less dangerous manifestations of parasympatholysis. Uneven and unpredictable absorption of quaternary ammonium compounds from the gastrointestinal tract is blamed for many of the toxic effects. The secondary amine, mecamylamine hydrochloride, is pharmacologically similar but has the advantage of being more completely absorbed when taken by mouth.[2] Unfortunately we have observed eight patients develop marked tremor, mental changes, or both while receiving mecamylamine. The toxic symptoms have appeared suddenly and without warning. Characteristically the tremor varied from coarse to flapping and involved all muscle groups, being particularly evident in the extremities; it disappeared during sleep and was worsened by voluntary activity, several times to the extent of preventing the patient from feeding himself. Mental changes have included irritability, agitation, depression, hallucinations, and lethargy progressing to coma. The only concomitant physical findings were hyperreflexia in two patients and hyperreflexia plus clonus and pathological toe and finger signs in another. No laboratory changes were noted.

All the patients involved had malignant stages of hypertension, as manifested by hemorrhagic and exudative retinitis, high fixed diastolic pressure, and proteinuria; moreover, in all of them the disease had progressed to the point of azotemia in the absence of clinically evident cardiac failure. Only one, however, had more than 100 mg. of nonprotein nitrogen per 100 ml. of plasma at the time when toxic symptoms appeared, and none had any of the other usual manifestations of clinical uremia, such as uremic pericarditis, colitis, pneumonia, or urea frost. Except for the first patient, there was no prior indication of cerebral vascular disease or other neurological dysfunction. Four patients had had no antecedent drug therapy, and four had previously received pentolinium (bi)tartrate and hydralazine hydrochloride for considerable periods. Because of the extremely grave prognosis, gradually increasing amounts of mecamylamine were given in an attempt to achieve the desired hypotensive effect. The maximum daily intake varied from 48 mg. taken orally to 430 mg. injected parenterally, and the total intake varied from 285 to 3,890 mg. over periods ranging from 2 to 63 days. Hydralazine, usually in large doses, was simultaneously administered orally, but clinically the patients' state bore little resemblance to that resulting from hydralazine toxicity.[3] Six patients had no residual tremor or mental changes a fortnight after their last dose of mecamylamine. The remaining two patients died soon after discontinuing the therapy, one in coma and one with renal failure. The severity of hypertension before any treatment is indicated for each patient in the table, which also gives some data on drug dosage and blood pressure before and during mecamylamine therapy. Additional information about individual patients follows.

From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, and Barnes Hospital. While this study was being made, Dr. Perry was an Established Investigator of the American Heart Association.

Report of Cases

CASE 1.—This patient was bedfast and blind when first seen. Although symptoms had begun only three weeks previously, there was physical and laboratory evidence of a malignant stage of hypertension (see table). During two months of hospitalization, her diastolic pressure became normal and remained so for the two years that she was treated with pentolinium and hydralazine. Over this interval her strength and vision improved until she could do housework and read large print. On rehospitalization for radical removal of a mammary carcinoma, funduscopic examination revealed no hemorrhages, exudates, or papilledema. However, after she had been without antihypertensive drugs for only 48 hours, this patient had 46 mg. of nonprotein nitrogen per 100 ml. of plasma, 2+ proteinuria, and a mean diastolic pressure of 148 mm. Hg. Her second hospitalization was stormy (see figure). On the morning of the sixth day after beginning the second course of mecamylamine, she was found markedly agitated and depressed, fidgeting and crying constantly. Hyperactivity of all deep tendon reflexes was present, and a marked coarse tremor of both arms and legs had appeared. Movements of the extremities persisted constantly when she was awake and were

exaggerated by voluntary activity. Simultaneously, definite pathological Hoffmann and Babinski signs plus marked ankle and patellar clonus were observed; inconstant toe signs and ankle clonus had been noted on her second admission to the hospital. There were no other new physical or laboratory findings. Circulating amounts of sodium, potassium, carbon dioxide, calcium, and phosphorus were normal. A magnesium level of 3.7 mg. per 100 ml. of serum was about twice the normal maximum and, since no magnesium had been administered, was regarded as possibly related to the azotemia. Diastolic normotension was rapidly reestablished with the administration of pentolinium and hydralazine plus 1,200 mg. of meprobamate (Equanil) per day. Except for leukopenia, no further clinical or laboratory abnormalities were noted in the subsequent two weeks, and there was a progressive, simultaneous disappearance of agitation, depression, tremor, and neurological findings. The number of granulocytes, which had decreased from 10,000 to 500 per cubic millimeter of blood during the 10 days of meprobamate therapy, returned to the previous value six days after the drug was withdrawn. There were no associated changes in blood pressure.

daily blood pressures shown for the hospital period were means of 6 to 24 determinations taken with the patient in the supine position just before the drugs were administered. Daily blood pressures shown for the period at home were means of five determinations taken with the patient in a sitting posture just before drugs were taken. The final month of each admission is not indicated, because it was a convalescent period when no further significant changes in blood pressure occurred.

Case 2.—This patient had had headaches and amblyopia for four months when oral therapy with mecamylamine and hydralazine was begun. After four weeks, near normotension was maintained, but it was associated with an unusually severe mental depression that caused the patient to require tube feeding. For two additional weeks, blood pressure and drug dosage remained essentially constant, with no significant change in azotemia or circulating electrolytes; then one morning the patient was found to be lethargic and disoriented. There was a marked coarse tremor which became more flapping in character during the day and which primarily involved the extremities. The patient became increasingly hyperactive, thrashing about constantly and jerking her arms and legs; she made

*Data for Eight Patients with Malignant Hypertension Who Developed Neurological Manifestations After Administration of Mecamylamine**

Case no.	1	2	3	4	5	6	7	8
Age, yr.	40	46	37	24	59	37	41	33
Sex	F	F	F	F	M	M	M	F
Period Before Therapy								
Mean supine systolic pressure, mm. Hg†	275	201	242	210	220	202	254	207
Mean supine diastolic pressure, mm. Hg†	160	121	162	163	151	133	171	136
Fundal hemorrhages, exudates, papilledema	HE‖	HEP	HE	HEP	HEP	0	HEP	HEP
Proteinuria	4+	2+	3+	2+	2+	±	3+	2+
15-min. excretion of PSP‡ (IV), %	8	1	25	0	20	35	15	15
Plasma nonprotein nitrogen, mg./100 ml. §	38	66	28	147	23	20	37	36
Period Before Mecamylamine Therapy								
Length of therapy, days	732	...	253	...	...	801	752	...
Mean pentolinium (bi)tartrate (oral), mg./day	670	...	970	...	...	860	3,100	...
Mean hydralazine hydrochloride (oral), mg./day	250	...	750	...	...	625	1,000	...
Mean supine systolic pressure, mm. Hg	141	...	157	...	...	149	164	...
Mean supine diastolic pressure, mm. Hg	79	...	98	...	...	97	99	...
Period of Mecamylamine Therapy								
Period of mecamylamine before symptoms, days	6	43	2	16	10	18	63	31
Total mecamylamine hydrochloride, mg.	645	1,804	795¶	805	285	970	3,890	1,345
Maximum mecamylamine (oral), mg./day	170	72	430¶	75	48	90	100	120
Concomitant hydralazine (oral), mg./day	600	750	1,800	150	600	600	1,000	900
Concomitant plasma nonprotein nitrogen, mg./100 ml.	55	76	82	87	40	134	34	16
Concomitant mean supine systolic pressure, mm. Hg	176	158	226	135	125	151	155	150
Concomitant mean supine diastolic pressure, mm. Hg	121	101	128	90	80	106	99	85
Period for symptoms to disappear after discontinuation of mecamylamine therapy, days	14	...	...	4	4	10	7	14

*Dosage and blood pressure data before administration of mecamylamine apply to period of optimal control immediately after initiation of antihypertensive therapy. Similarly, dosage and blood pressure as well as nonprotein nitrogen data during mecamylamine therapy apply to period immediately before discontinuation of mecamylamine therapy when dosage was maximal.

† Means of from 12 to 35 supine readings.

‡ PSP = phenolsulfonphthalein.

§ Maximum normal concentration of nonprotein nitrogen in plasma is 25 mg./100 ml. by technique of Somogyi (J. Biol. Chem. 86:655, 1930).

‖ H = hemorrhages; E = exudates; P = papilledema.

¶ Intramuscularly.

In the figure blood pressure and drug intake are shown plotted against time for this patient. The left part of the curve deals with the hospitalization in 1954 and shows the hypertension before therapy as well as the control achieved by pentolinium and hydralazine. The right part of the curve deals with the course in 1956 and begins 10 days before the second hospitalization, during which there were three episodes of hypertension. The first episode occurred when all medication was stopped in error just prior to entry, the second occurred after operation when measures for controlling the blood pressure were temporarily discontinued, and the third occurred when drugs were withdrawn in hopes that urinary retention would vanish. The extremely rapid rise in blood pressure when medication was withheld after two years of excellent control is striking. Tolerance to the combination of ganglionic blocking agents and hydralazine after temporary cessation of therapy has been noted.[4] The ineffectiveness of previously antihypertensive doses of pentolinium is evident, and it was even more striking in the third patient.

All medication indicated in the figure was oral, and the doses were given in terms of the hydrochlorides for mecamylamine and hydralazine and the bitartrate for pentolinium. All

some coordinated movements, such as pulling her hair. All antihypertensive medication was stopped, and 375 mg. of amobarbital (Amytal) sodium was given intravenously during a period of 30 minutes, without obvious effect. Neurological examination revealed only hyperreflexia. Except for the lowered blood pressure, no other changes in physical signs had occurred since admission. Circulating amounts of sodium and carbon dioxide were normal. There were 9,500 leukocytes per cubic millimeter of blood, without any preponderance of young granulocytes. Two blood cultures were sterile, but the Proteus organism, present in the urine for several weeks, persisted there. The pressure of the cerebrospinal fluid was not increased, nor was there any pleocytosis or excess amount of protein. Within 36 hours the temperature gradually rose to 41 C (105.8 F) and the lethargy deepened into coma, with the only movement being marked flapping tremor of arms and legs. During the remaining 12 hours of life normotension was sustained without evidence of shock; there was no increase in azotemia; blood cultures continued sterile; leukocytosis failed to appear; and the concentration of circulating electrolytes was not altered. At autopsy no lesion of the nervous system was found. There was advanced arteriolar nephrosclerosis, with

a total renal weight of 180 Gm., and cardiomegaly, with a total cardiac weight of 400 Gm.; in addition, moderate and advanced arteriosclerosis was widespread.

CASE 3.—This patient began treatment with pentolinium and hydralazine a year after a bilateral thoracolumbar sympathectomy for a malignant stage of hypertension. Eight months later she had largely discontinued therapy and was rehospitalized, with a mean supine blood pressure of 250/150 mm. Hg, hemorrhagic and exudative retinitis without papilledema, 2+ proteinuria, and 59 mg. of nonprotein nitrogen per 100 ml. of plasma. When 1,800 mg. of pentolinium and 1,800 mg. of hydralazine administered orally per day failed to lower her diastolic pressure, a parenteral injection of mecamylamine every two hours was substituted for pentolinium, without change in the hydralazine intake. The mecamylamine dosage was rapidly increased for two days, but the drug was withdrawn after successive doses of 100, 110, and 120 mg. produced obtundity, somnolence, and hallucinations, without diminishing the hypertension, altering the normal concentration of circulating electrolytes, or causing other evident clinical change. Within 24 hours the mental abnormalities had cleared. Four days after the last dose of mecamylamine, twitching of the face and upper extremities was observed; however, by then the nitrogen retention had doubled. The coarse tremor worsened during the next week as the patient became anuric. Autopsy revealed chronic glomerulonephritis without arteriolar necrosis. The heart weighed 420 Gm., and there was anasarca but no anatomic lesion of the nervous system.

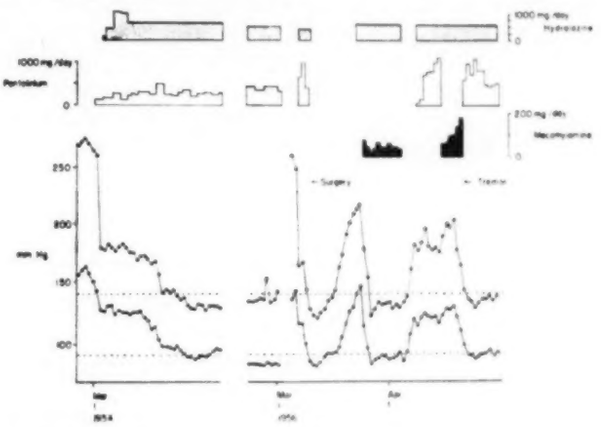
CASE 4.—This patient was markedly azotemic without cardiac insufficiency. Sixteen days after starting mecamylamine and hydralazine therapy, she was normotensive and less azotemic; however, at this time a moderately coarse, generalized tremor, which did not interfere with normal activity, suddenly appeared. Within three days of the substitution of pentolinium as the ganglionic blocking agent, the tremor had lessened considerably; at this time there was approximately 0.1 mg. of mecamylamine per 100 ml. of plasma and 0.4 mg. of the agent per 100 ml. of urine. In another 24 hours the tremor had vanished, and no more of the drug could be measured in body fluids. No concomitant changes were noted. After a month of normotension maintained with orally administered pentolinium and hydralazine, the patient returned home, her nonprotein nitrogen level being only 36 mg. per 100 ml. of plasma.

CASE 5.—This patient was found to be alternating between extreme euphoria and severe depression, manifested by considerable crying, on the 10th day after mecamylamine and hydralazine therapy had been instituted. Moreover, he had had hallucinations involving a divine visitation the preceding night. Administration of mecamylamine was stopped immediately, but it was four days before the mental changes vanished as suddenly as they had come. Immediate reinstitution of the previous doses of mecamylamine has maintained normotension for six months and has provoked no further symptoms, the patient in the meantime having returned to his job. A tremor was never observed. The only additional change has been a persistent leukopenia, which was first noted after the patient was temporarily given meprobamate for his mental symptoms and which was not present on his admission to the hospital.

CASE 6.—This patient, when first seen, had asymptomatic hypertension which was initially well controlled. After an absence of two years, he was found to have a mean resting diastolic pressure of 130 mm. Hg, hemorrhagic and exudative retinitis with papilledema, 2+ proteinuria, and 79 mg. of nonprotein nitrogen per 100 ml. of plasma. Oral therapy with mecamylamine and hydralazine resulted in lower blood pressure and greater nitrogen retention. On the 18th day of mecamylamine therapy, the patient became extremely agitated and depressed, allowing no one in his room. The following day a generalized coarse tremor and hallucinations appeared; the patient saw reptiles and rodents, which he recognized as unreal. No further abnormal physical signs were noted. The concentration of circulating electrolytes was normal except for an elevated magnesium level of 3 mg. per 100 ml. of serum. After mecamylamine was replaced by pentolinium, the hallucinations lasted only 24 hours, and within 10 days the agitation and tremor had disappeared. The patient was discharged against advice, with slowly increasing renal failure.

CASE 7.—This patient had required the administration of extremely large doses of hydralazine and pentolinium for two years to control his blood pressure satisfactorily. Therefore, orally administered mecamylamine was substituted as the ganglionic blocking agent. Seven weeks after the change in therapy increasing irritability began, and two weeks later a tremor developed which prevented the patient from writing. There were no other obvious concomitant changes. Administration of mecamylamine was promptly discontinued, and chlorisondamine (Ecolid) chloride therapy was begun. Within a week the tremor and irritability were appreciably less, and in a fortnight they were gone. This patient was the only one whose toxic symptoms did not appear while he was in the hospital.

CASE 8.—This patient had few symptoms. Normotension was achieved after two weeks of oral therapy with mecamylamine and hydralazine and was maintained by a constant dosage of the drugs for an additional fortnight until the sudden appearance of a progressively increasing tremor of all muscle groups. Within 48 hours the tremor had become particularly marked in the upper extremities, where it assumed a flapping character and prevented normal eating. There were no evident mental changes, and hyperreflexia was the sole associated sign. Two weeks after antihypertensive medication was discontinued, the patient was discharged from the hospital against advice, without symptoms but with an uncontrolled malignant stage of hypertension. There was no abnormal nitrogen retention when the tremor was observed, although azotemia was present until the hypertension was controlled.



Blood pressure and drug intake of patient in case 1.

Comment

The mechanism by which a secondary amine effects ganglionic blockade is uncertain; that its configuration competitively inhibits the quaternary ammonium ion of acetylcholine would be surprising. The neurological changes, particularly the flapping tremor, are suggestive of those seen in hepatic failure and correlated with amounts of circulating ammonia.[5] There was no cogwheel rigidity or other sign of Parkinsonism, such as has occasionally been observed after the use of ataraxic agents such as reserpine.[6] It should be emphasized that all the patients discussed here, except the seventh, were considered to be critically ill when therapy was started and all presented extremely involved and complicated problems. Not only did they have severe malignant hypertension with azotemia, but also large amounts of hydralazine had been administered. That some of the observed neurological manifestations were related to nitrogen retention or cerebral arteriosclerosis is possible; however, there were none of the non-neurological findings ordinarily ascribed to uremia and no prior evidences of signifi-

cant vascular disease in the brain. In our experience the tremor and the mental changes which have been cited rarely accompany malignant stages of hypertension and then only just before death, a condition manifestly absent in the six surviving patients. We have not seen similar toxic reactions in these or other patients receiving large amounts of quaternary ammonium compounds and hydralazine over long periods of time. The failure to reproduce symptoms in the second patient by reexposure to the previous dose of mecamylamine might be related to improved renal function. Attempts to reinduce the syndrome in the others by a second course of mecamylamine were precluded either by the precarious state of the patient or by his express desire. That toxicity was not seen without a large intake plus renal dysfunction suggests that combination of excessive absorption and poor excretion is required. Further factors may be involved, since at least one azotemic patient has daily taken 150 mg. of mecamylamine by mouth for four months without trouble.

Summary

Eight patients with malignant stages of hypertension that had progressed to azotemia received from 48 mg. orally to 430 mg. parenterally of mecamylamine per day plus large doses of hydralazine. In from 2 to 63 days a coarse tremor occurred in seven patients and mental changes in five. Except for two patients who died soon after the symptoms appeared, withholding the drug resulted in disappearance of the symptoms within two weeks.

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The mecamylamine used in this study was supplied as Inversine by the Merck Sharp & Dohme Division of Merck & Co., Inc., of West Point, Pa.

The method used for estimating levels of mecamylamine in body fluids was worked out by J. E. Baer, of the Merck Sharp & Dohme Division of Merck & Co., Inc., West Point, Pa.

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MARCH HEMOGLOBINURIA

REPORT OF FIVE CASES IN STUDENTS AT OHIO STATE UNIVERSITY

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• *Dark-colored urine and painfully swollen muscles were the essential complaints of five otherwise healthy, athletic students at the Ohio State University. The manifestations included albuminuria in all cases; in the most severe case, casts and red blood cells were found in the urine and the temperature went up to 100F (37.8 C). The common causative factor proved to be recent exhausting muscular exercise, and recovery was spontaneous. The condition is not believed to have been identical with that described by other authors as march hemoglobinuria but a new syndrome termed "exercise myohemoglobinuria."*

March hemoglobinuria has been defined as "a condition in which physical exertion gives rise to the passage of a red urine containing hemoglobin in solution." A comprehensive review of the subject was given by Gilligan and Blumgart of the Harvard Medical School in 1941.[1] Up to this time there had been only 40 cases reported in the literature, mainly German. The condition was first described by Fleischer[2] in 1881; 29 cases were precipitated by strenuous walking, while those in 11 athletes followed strenuous runs. During the decade after 1941, 33 more cases were reported. Chaiken and associates[3] reported two new cases in 1953, increasing the total to 75.

Report of Cases

Case 1.—This patient, a 21-year-old white male weighing 165 lb. (74.8 kg.), was first seen in the Ohio State University Health Service on Jan. 18, 1954. His chief complaints were painful and swollen muscles and dark-colored urine. Urinalysis showed 1+ albumin, 3+ hyaline and granular casts, and 2+ red blood cells. The patient was asked to bring in a first morning urine specimen on the 19th. This showed 2+ albumin, 4+ granular and hyaline casts, and 2+ red blood cells. The patient's temperature was 100 F (37.8 C). Additional history revealed that approximately 60 hours prior to this visit the patient had been compelled by his active fraternity brothers to get out of bed three times during the night and each time for 30 to 45 minutes to do push-ups, knee-bends, and so forth. At this visit, because of the fever and urinary findings of our laboratory, we considered the possibility of an acute glomerular nephritis and hospitalized the student for evaluation.

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Read before the Ohio College Health Association at the Ohio State University, Columbus, April 20, 1956.

On the patient's admission to the hospital, urinalysis showed 100 mg. of protein per 100 cc., occasional coarse and finely granular casts, and 1 to 3 white blood cells and occasional red blood cells per high-power field. Other laboratory findings were normal. On the second hospital day there was 5 mg. of protein per 100 cc., and the urine was clear. The patient was discharged the third day with a diagnosis of march hemoglobinuria.

Case 2.—This patient, a 21-year-old white male weighing 168 lb. (76.2 kg.), visited the Ohio State University Health Service on Feb. 8, 1954. His temperature was 98.4 F (36.9 C), and he complained of red-colored urine for the past 24 hours and stiffness and painful swelling of the thigh muscles. He had done 159 knee-bends approximately 60 hours before coming to the University Health Service. Urinalysis showed 1+ albumin, 2 to 3 white blood cells per high-power field, and 1+ squamous epithelial cells. A diagnosis of march hemoglobinuria was made.

Case 3.—This patient, a 20-year-old white male weighing 165 lb., visited the Ohio State University Health Service on Feb. 8, 1954. His temperature was 98.6 F (37 C). He had the same complaints as the student in case 2 as a result of having done 150 knee-bends. Urinalysis showed a trace of albumin and 4 to 5 white blood cells per high-power field. Both this patient and the patient in case 2 had been doing knee-bends for fun to see who could do the most.

Case 4.—This patient, a 20-year-old male weighing 158 lb. (71.7 kg.), was first seen in the University Health Service on March 3, 1955. His chief complaints were painful and stiff arm muscles and dark-colored urine. His temperature at this time was 97 F (36.2 C). Three days prior to the visit he had "worked out" for an hour to "get in condition" by doing "about" 200 push-ups. The muscles of both upper arms were swollen and tense. Urinalysis showed 3+ albumin, 1+ granular casts, and 20 to 30 white blood cells per high-power field. The muscle soreness and swelling did not disappear until the seventh day.

Case 5.—This patient, a 20-year-old white male weighing 135 lb. (61.2 kg.), visited the Ohio State University Health Service on Feb. 10, 1956. His chief complaints were painful and swollen muscles and dark-colored urine. History revealed that for the previous three nights he and his fellow pledges had been made to do push-ups, sit-ups, and general calisthenics for various periods to the point of exhaustion and with no sleep. He noted the dark-colored urine approximately 48 hours after beginning the exercises. The biceps, triceps, deltoids, and pectoral muscles were tense and swollen. Urinalysis showed 4+ albumin, occasional granular casts, and 0 to 1 white blood cells per high-power field and was negative for occult blood. A diagnosis of "exercise myohemoglobinuria" was made. The patient was asked to return to the Health Service but failed to do so. He was also asked to send any of his friends who had been through the same ordeal to the Health Service. None showed up, probably because we knew the name of the fraternity and the members feared reprisals.

From the table it is concluded that the patient in case 1 had the roughest time, as he had fever and red blood cells in the urine. We cannot explain the presence of white blood cells in the urine, except as due to irritation of the bladder or kidneys from the exercise. The possibility of previous genitourinary infection was not explored, but, since no bacteria were revealed in any patient and since the urine was within normal limits in two to three days without medication in all these cases, it seems reasonable to conclude that there was no infectious process.

Comment

These five cases of march hemoglobinuria syndrome present a similar picture: (1) painful, swollen muscle groups; (2) dark, coffee-colored urine; and (3) history of excessive, strenuous exercise within a short period of time. Urinalysis in all five cases showed albuminuria and varying numbers of white blood cells. Only the patient in the first case had any fever and any red blood cells in the urine. All the students were young, healthy males of the athletic type.

It is interesting to note that these five cases fall into three categories: (1) fraternity initiation hazing; (2) competition between two students for fun to see who had the most endurance; and (3) individual attempt to get into better condition by too strenuous and concentrated physical exercise.

In the first case we were misguided because of an inadequate history on the first visit. The temperature of 100 F with the urinary findings made us think of an acute glomerular nephritis, even though we knew about the patient's previous strenuous exercise. He was then hospitalized with the possibility of that diagnosis. We had all heard of march hemoglobinuria, but none of us among the more recent staff members had seen a case. One probable case had been seen in the department in the late 1930's, but it had not been studied or diagnosed and recorded as such. After the diagnosis of the first case had been made in the hospital, we were alerted to the possibility of this syndrome and subsequently made the correct diagnosis of the other four cases. Treatment in all these cases consisted of bed rest if the patient desired it, administration of aspirin for the alleviation of muscular soreness, and the prohibition of additional exercises.

*Similarity of Urinary Findings in Five Cases of March Hemoglobinuria**

	Case No.				
	1	2	3	4	5
RBC	++	...	...	...	...
WBC	+	2-3	4-5	20-30	0-1
Granular casts	++++	...	...	+	+
Albumin	++	+	+	+++	++++

* All patients had painful, swollen muscles and dark-colored urine. Bacteria were not found in urine of any patient. Patient in case 1 was only one with elevated temperature (100 F).

Palmer and Mitchell [4] give a general classification of the paroxysmal hemoglobinurias as follows: (1) paroxysmal hemoglobinuria from chilling (syphilitic type); (2) paroxysmal nocturnal hemoglobinuria in chronic hemolytic anemia (Marchiafava-Micheli disease); (3) favism (sensitivity to products of the plant Vicia faba [fava]); (4) myoglobinuria ("paralytic hemoglobinuria"); (5) march hemoglobinuria; and (6) miscellaneous (toxic) hemoglobinurias, as in severe infections, some poisonings, and incompatible transfusions. Our five cases do not fall into any of these general categories, so we might add a seventh category —myohemoglobinuria, arising from the breakdown of myohemoglobin due to severe, strenuous exercise over a short period of time, manifesting itself by painful, swollen muscle groups with dark-colored urine.

In all the literature available to review, this type of hemoglobinuria has not been discussed. The patients in the cases reviewed have shown a spontaneous hemoglobinuria within a few hours after the exercise. In some patients it has been possible to reproduce the syndrome, while in others it has not. Unfortunately we did not have the privilege of asking our students to repeat their performances, nor did we have the laboratory facilities for doing the complete blood, urine, and

other studies done by other authors. We must rely on our relatively less complete laboratory and clinical findings.

In the past, the syndrome has almost always been associated with exercises performed in the erect posture, such as marching or running. The presence of a lumbar lordosis or the assumption of a lordotic posture has been said to be a contributing factor in many of these cases. Both these assumptions were found to be false in a case reported by Chaiken and associates [3] of a soldier who developed hemoglobinuria after crawling through the infiltration course. The soldier had had two similar episodes after swimming. It was the opinion of these authors that hemoglobinuria never occurred in the absence of exercise. After their paper had been submitted for publication, the soldier mentioned developed a spontaneous recurrence of hemoglobinuria without exercise. Prior to this time, he had been in apparent remission for nine months after corticotropin (ACTH) therapy and had been performing exercises in all positions without a recurrence of hemoglobinuria.

The mechanism of hemoglobinuria is still unknown, but it is generally considered that there is blood destruction intravascularly, i. e., that all the hemoglobin from red blood cell destruction appears in the plasma, giving rise to hemoglobinemia. We believe that in our cases there was a breakdown of the muscle fibers due to the extreme and excessive exercise, so that the myohemoglobin was released into the blood plasma and then excreted through the kidneys, causing the dark-colored urine, which gave the diagnosis of march hemoglobinuria. We believe that this syndrome should be called "exercise myohemoglobinuria."

In the cases of march hemoglobinuria completely studied by Gilligan and Blumgart,[1] it was found that the hemoglobin appeared in the urine one to three hours after exercise; thus, the disorder developed almost immediately. In our cases the dark-colored urine appeared 24 to 48 hours after exercise; the urine was clear 48 to 72 hours after the onset of the discoloration. We think that this is an important point in the diagnosis of this type of hemoglobinuria.

It is interesting to note that all the patients whose cases have been reported in the literature have been young, athletic white men. No cases have been reported among women or in any other race than the white. It would be interesting to conduct an experiment with a group of college students, male and female and of different races, having them do excessive, strenuous exercises, such as push-ups, sit-ups, and knee-bends, for a short period of time to see if the myohemoglobinuria could be duplicated, as in the five students we have seen.

We feel sure that other students with march hemoglobinuria have come to the Health Service, but we have missed them, either because of inadequate history taking or because of failure of the student to present all the facts. We also feel that there have been students with this disorder at the university who have not visited the Health Service because of the mildness of the symptoms or because of fear of getting into trouble with their fraternities, where such hazing is not supposed to occur. We would like to point out that this type of hemoglobinuria is a benign condition with short duration, but it should be recognized and differentiated from the other types enumerated earlier in this discussion.

Summary and Conclusions

Five cases of spontaneous hemoglobinuria were found among Ohio State University students. All cases have been associated with excessive, strenuous exercises within a short period of time. Complaints of painful, swollen muscle groups and coffee-colored urine developed 24 to 48 hours after exercise. The findings in the five cases are submitted as a new syndrome called "exercise myohemoglobinuria."

Addendum

During the winter quarter, 1957, three additional cases of exercise myohemoglobinuria were seen in the University Health Service. These three male students had participated in fraternity initiations.

J. W. Wilce, M.D., Director, Health Service, Ohio State University, and Karl H. Feistkorn, M.D., of the Clinical Staff, cooperated in making the report of these five cases.

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Tendon Tunnel Syndromes.—Wherever a tendon crosses a joint it needs a fibrous tunnel to prevent it from bow-stringing. Within this tunnel the tendon is covered by a synovial sheath to allow it to slide smoothly. Inflammation of the synovial sheath (tenosynovitis) results in painful movement. Normal tendon action, however, is more often impeded by thickening of the fibrous sheath or of the tendon itself; in either case there is not enough space in the tunnel. The term "stenosing teno-vaginitis" is sometimes used to describe these tendon-tunnel syndromes. The commonest examples are clicking finger, trigger finger, clicking thumb, congenital flexion of the thumb, and de Quervain's disease. Nerves also are confined within fibrous tunnels where they cross joints. There are two sites where the tunnel may be too small: at the elbow, giving rise to ulnar neuritis, and in front of the wrist, leading to median neuritis.—A. G. Apley, M.B., Tunnel Syndromes in the Upper Limb, *The Practitioner,* December, 1956.

STUDIES ON SIGNIFICANCE OF BIOLOGIC FALSE-POSITIVE REACTION

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• *The Treponema pallidum immobilization test, a specific means of diagnosing the biologic false-positive reactor, will separate syphilitic from non-syphilitic patients, within minor limitations. However, the diagnosis of biologic false-positive reactor raises significant questions concerning the patient. Of 555 patients having this diagnosis, 21.6% had systemic disease in one form or another, 2% having systemic lupus erythematosus. Alertness to the finding of a biologic false-positive reaction is indicated, especially in young women; such findings require careful follow-up, including a search for vague signs and symptoms of a previously undiscovered systemic illness.*

Sufficient experience has now accumulated to establish that the results of the Treponema pallidum immobilization test will separate the syphilitic from the biologic false-positive reactor within minor limitations to be mentioned shortly. The evidence on which this statement is based has been previously reported both by our group [1] and by others.[2] Included in this evidence are the positive results of the Treponema immobilization test in patients with proved syphilis (except where treatment was given early in the course of the disease), the reproducibility of the results in repeated specimens from the same patient, and the consistently negative results in patients presumed to be normal and in those with diseases other than the treponematoses. In our experience there is a probable error of about 1.2%, which for a biological test justifies the conclusion that the test is highly specific.

Our limited experience with the T. pallidum complement-fixation test, which we recently reported at the International Symposium on Venereal Diseases, suggests that this test may also have a high order of specificity. This agrees with the experience with this test reported by others.[3] This test is based on a different antibody from that of the Treponema immobilization test, which may result in slight differences in end-results. Once these are fully established, the complement-fixation test should prove to be of great value, as it is simpler than the Treponema immobilization test and thus more suited to use in a routine laboratory.

In the course of our studies with the Treponema immobilization test we were impressed with the high incidence of biologic false-positive reactions in patients with the collagen diseases, especially systemic lupus erythematosus. These cases were largely found among patients who, because of their illness, had required hospital admission. These findings were published in 1954.[1] The probable existence of biologic false-positive reactions in patients with systemic lupus erythematosus had been recognized by observers [4] for a number of years. Moore and Mohr,[5] in 1952, emphasized the collagen group of diseases as a cause of biologic false-positive reactions in a study controlled by the Treponema immobilization test.

Aware of the potential seriousness of the diagnosis of biologic false-positive reactivity and aware of the probable relative increase in this diagnosis as active syphilis becomes less prevalent, we started the study to be reported here. This study was designed to gather evidence to assist the physician in the management of the individual patient with biologic false-positive reaction. Our aim was to study as large a group as feasible, gathered not only from hospital patients but also from patients discovered to have biologic false-positive reactions in routine examination. By this means the findings should more nearly represent the over-all picture and not be outweighed by the findings in those already ill.

The majority of our patients were studied in the Vanderbilt Clinic and the Presbyterian Hospital. The remainder were studied by various physicians and the results of these studies made available to us. All of the Treponema immobilization tests were done in our laboratory at Columbia University, and serologic tests for syphilis were done on the same samples in the same laboratory. Results of serologic tests for syphilis done elsewhere were used to round out the picture of the duration of the positive serologic test for syphilis.

TABLE 1.—*Classification of Patients with Positive Serologic Tests for Syphilis (STS) and Negative Treponema Pallidum Immobilization Tests*

Group		Known Duration of Positive STS Findings: More than 6 Mo.	Less than 6 Mo.	Temporary	Total: No.	Total: %
Systemic disease		57	63	0	120	20.2
No systemic disease		188	247	24	459	77.3
Old syphilis, treated early		9	6*	0	15	2.5
Total	No.	254	316	24	594	100
	%	42.8	53.2	4.0	100	

* Negative STS after original treatment. Present positive findings of less than six months' duration.

Material

In table 1 there are listed the findings in 594 patients who had positive serologic tests for syphilis but negative Treponema immobilization tests. They are divided into two major groups. The first group had a systemic disease, and in the large majority of these patients the positive serologic test for syphilis was discovered in the course of examinations on hospital admission. The second major group were patients whose positive

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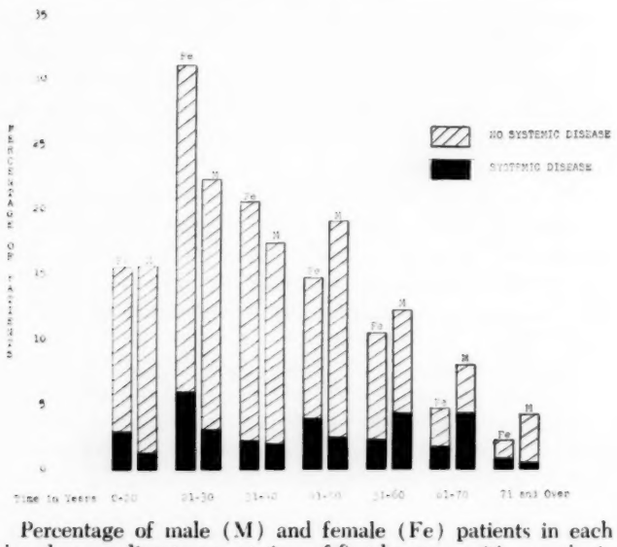
serologic test for syphilis was discovered as a result of routine tests taken for admission to the armed forces, jobs, marriage, and other reasons. Twenty-four patients with temporary false-positive reactions are listed but will not be further considered in this paper. Fifteen patients who were treated in the early stages of syphilis, often years ago, who today have positive serologic tests for syphilis and negative Treponema immobilization tests, are listed and will be discussed later.

The groups are further divided into those whom we have followed for more than six months and in whom the serologic test for syphilis has remained positive and those whom we have followed for less than six months. Although no definite conclusions can be drawn from the findings in the groups in which the known duration of the positive reaction is less than six months, they are of value in determining the known age of onset of the positive reaction, the sex of the person tested, and the presence or absence of systemic disease. Careful history taking and physical examination were done in all patients to determine



Percentage of male (M) and female (Fe) patients in each decade according to age at time of first known positive serologic tests for syphilis.

any evidence of previous syphilitic infection or vague signs of systemic disease. All of the usual causes of temporary false-positive reaction were excluded. Three patients with leprosy or malaria and in whom the duration of the positive reaction was unknown were not listed. From our experience we think it is reasonable to presume that the large majority of these patients will prove to have persistent biologic false-positive reactions. There were 57 patients with systemic disease among 245 patients with persistent biologic false-positive reactions. Thus, 23.2% of this group had a systemic disease. The percentage of patients having systemic disease is 20.3 of the group in which the known duration of the positive serologic test for syphilis with a negative Treponema immobilization test is less than six months. There is thus little difference in the percentage with systemic disease in the two groups.

The 15 patients listed as having had syphilis that was treated early are excluded from the following tables. They are of interest since, were the history not known, they would be classified as biologic false-positive reactors. In fact, seven patients were treated for early syphilis a number of years ago, the earliest in 1917 and the rest scattered through the years until 1946. After treatment, and often for many years, the serologic test for syphilis remained negative, only recently becoming positive. These presumably could be biologic false-positive reactors, as there was no evidence of reinfection. Five patients were treated in the past three years, probably early enough in the course of the disease to prevent the development of the Treponema immobilization antibody. In fact, one of these patients has a positive T. pallidum complement-fixation test to support this view. The remaining three patients have had positive serologic tests for syphilis since their original treatment.

In the figure, the distribution of the patients thought to have biologic false-positive reactions is presented to show the sex and the age at which the positive reaction was first discovered. Although the sex and age findings for the group in which the known duration of the positive reaction was more than six months and the group in which it was less than six months have been combined in preparing the figure, these groups were analyzed separately. The percentages of males and females in the two groups showed no statistically significant differences except in the patients with systemic disease. Of the patients with positive serologic tests for syphilis for more than six months, 84% were females, while in the group where the known duration of the positive reaction was less than six months the percentage of females was 67%. The ratio of females to males is not evident from the figure, as it is prepared from percentages. There was, however, a decided preponderance of females over males. There were 395 females (71%) to 160 males (29%) in the entire series. In the majority of patients the age of the known onset of the positive serologic test for syphilis, as can be seen from the bar diagram, is from 20 to 50 in both sexes. The onset of the positive reaction in the females was found to occur particularly frequently between the ages of 20 and 30.

In table 2 are listed the findings in percentages of the three serologic tests for syphilis performed on the same specimens in which the result of the Treponema immobilization test was negative. The percentage of patients in whom the Mazzini, Venereal Disease Research Laboratory, and Kolmer tests were all positive is somewhat higher in the group with systemic disease than in those without systemic disease. The group in which the Mazzini test alone was positive, while the Kolmer and Venereal Disease Research Laboratory tests were negative, was the second largest. The necessity for including the results of the Mazzini test was borne out in a study previously published.[6] It showed that in 1,300 specimens from patients with positive Treponema immobilization tests the Mazzini test was negative in only 5%, while the Kolmer and Venereal Disease Research Laboratory tests were negative in approximately 20%.

In table 3 are listed the systemic diseases that in this study were associated with a biologic false-positive reaction. Some of the diagnoses are of necessity vague and are purposely so listed. The following diseases were also found, with one female patient having each disease: congenital hemolytic anemia, cryoglobulinemia, lymphatic leukemia, infectious mononucleosis, pemphigus vulgaris, histoplasmosis, glomerulonephritis, post-toxemic brain damage, meningioma, postencephalitic Parkinsonism, optic (retrobulbar) neuritis, subarachnoid hemorrhage, para-aortic mass, and adrenal cortical hypofunction (Addison's disease). The following diseases occurred in one male patient each: pernicious anemia, hemolytic anemia with cold agglutinins, Vogt-Koyanagi syndrome, fibrosis and calcification of the pericardium, lower motor neuron damage, and metastatic carcinomatoses.

Twelve patients had systemic lupus erythematosus, as established by the finding of the L. E. cell. Nine had rheumatoid arthritis, and 11 had diseases of the liver. Of these 11, 6 had Laennec's cirrhosis and one each, amebic hepatitis, obstructive jaundice, and coarse nodular (postnecrotic) cirrhosis. The remaining two had viral hepatitis. The patients listed as having rheumatic heart disease were patients with history of that disease and not patients with acute attacks at the time our tests were taken. Two patients listed as diabetics also had myocardial infarction, and one patient listed as having discoid lupus erythematosus also had diabetes.

Analyzed, but not listed, were the ages at which the serologic test for syphilis was first found to be positive. In the group with systemic lupus erythematosus there were six patients, all females, who developed their disease from age 25 to 30. The test had been known to be positive from 2 to 21 years, the average being about 6 years. In the six patients with this disease in whom the duration of the positive serologic test for syphilis is unknown, the age at the verified onset of the disease varied from 11 to 54 years. All were females. Of the patients listed as having rheumatoid arthritis, seven were 45 to 70 years of age and two were near 30 years of age. The serologic test for syphilis had been known to be positive from 1 to 15 years. The group of patients with myocardial infarction were above 50 years of age with one exception. The ages of the remainder varied, depending largely on the diagnosis, the group with vague symptoms being 20 to 40 and the group in which the diagnosis was definite being older.

TABLE 2.—*Results of Mazzini, Venereal Disease Research Laboratory (VDRL), and Kolmer Tests in Biologic False-Positive Reactors With and Without Systemic Disease*

Mazzini	VDRL	Kolmer	Systemic Disease		No Systemic Disease		Total	
			No.	%	No.	%	No.	%
Pos.	Pos.	Pos.	54	45.0	149	34.3	203	37.6
Pos.	Neg.	Neg.	27	22.5	183	42.1	210	37.8
Pos.	Pos.	Neg.	18	15.0	36	8.3	54	9.7
Pos.	Neg.	Pos.	12	10.0	48	11.0	60	10.8
Neg.	Pos.	Pos.	0	0	1	0.2	1	0.2
Neg.	Pos.	Neg.	2	1.7	3	0.7	5	0.9
Neg.	Neg.	Pos.	1	0.8	14	3.2	15	2.7
Pos.	Pos.	AC*	6	5.0	1	0.2	7	1.3
Total			120	100	435	100	555	100

* Anticomplementary.

A variety of laboratory tests were performed on certain of the patients both with systemic and with nonsystemic disease in an effort to find which tests should be done in a person with an uncomplicated biologic false-positive reaction. These included complete blood cell counts, urinalyses, cold agglutinations, protein partitions, heterophil antibody agglutinations, and Brucella agglutinations; cephalin-flocculation, thymol-turbidity, Coomb's, and L. E. tests; determination of antistreptolysin titers, erythrocyte sedimentation rates, electrophoretic patterns, and basal metabolic rates; electroencephalographic and electrocardiographic studies; and determination of blood cholesterol, alkaline phosphatase, cryoglobulin, and bilirubin levels. The number of these tests has been limited largely because of expense. An analysis of our findings shows that the cephalin-flocculation and thymol-turbidity tests, protein partition, and determination of the sedimentation rate are the studies in which abnormalities will most probably be found. Approximately one-third of the patients with no systemic disease in whom these tests were done showed abnormal findings. This was to be expected, as all of these tests may be influenced by abnormal globulins. As was to be anticipated, approximately three-fourths of the patients with systemic disease had abnormal findings in this group of tests.

TABLE 3.—*Systemic Diseases Associated with Biologic False-Positive Reaction*

	Serologic Test for Syphilis Positive			
	More Than 6 Mo.		Less Than 6 Mo.	
	Female	Male	Female	Male
Systemic lupus erythematosus with positive L.E. cells	6		6	
Diseases of liver	2	1	4	4
Rheumatoid arthritis	7	1	1	
Rheumatic heart disease	4	1	3	1
Diabetes mellitus	2		3	1
Myocardial infarction			2	3
Tuberculosis	3		1	
Periarteritis nodosa			1	1
Discoid lupus erythematosus			1	1
Subacute bacterial endocarditis		1		1
Convulsive disorders	4			1
Possible collagen disease	3		4	
Possible multiple sclerosis	4			
Chronic arthritis	2		2	1
Arthritis with facial eruption	1		1	
Dizziness, headache, vertigo		2	1	
Hepatosplenomegaly and pleurisy	1	1		
Fever of unknown origin			1	1
Vague symptoms	2		4	2
Other*	7	2	7	4
Total	48	9	42	21

* See text.

Leprosy is the one disease of known etiology associated with a high degree of biologic false-positive reactions. This disease thus offered an opportunity to study the question whether the biologic false-positive reaction is coincidental or related to some abnormal

globulin. Sister Hilary Ross [7] of the Carville Leprosarium kindly made available the results of cephalin-flocculation and thymol-turbidity tests and protein fractionations in a group of 35 patients with lepromatous leprosy and negative serologic tests for syphilis and in 44 patients with the same disease and positive serologic tests for syphilis. The group of 35 patients with negative reactions showed 6 negative cephalin-flocculation and 22 negative thymol-turbidity tests, while the group of 44 patients with positive reactions showed only 2 negative cephalin-flocculation tests and 14 negative thymol-turbidity tests. Thus, these tests were found to be positive in a high percentage of patients with negative serologic tests for syphilis but in a somewhat higher percentage when the serologic test was positive. Twice as many patients with positive serologic tests for syphilis showed increased alpha and gamma globulins as did those patients with negative reaction. The significance of this requires further study.

Comment

The Treponema immobilization test has in the last six years given physicians for the first time a specific means for making the accurate diagnosis of biologic false-positive reaction. Once this diagnosis is made, the question naturally arises as to the significance of this diagnosis in a given patient. That it is a diagnosis of possibly serious import is evident from even a casual glance at the figures presented here. Of 555 patients reported here, 21.6% already had systemic disease in one form or another.

The role of systemic lupus erythematosus, as being responsible for a portion of the systemic disease associated with biologic false-positive reactions, has been emphasized by a number of investigators, including those of our group. Since the discovery of the L. E. cell phenomena a few years ago, much experience has accumulated concerning this disease. Haserick and Long [8] and others [5] have reported that many of the patients with systemic lupus erythematosus had passed through a period of varying length in which their symptoms and signs resembled many diseases and definite diagnosis was not possible. This has been called the lupus diathesis.

Two per cent of the patients reported here had systemic lupus erythematosus. Two per cent of the patients with biologic false-positive reactions reported by Ledbetter [9] had collagen disease. If we include all those patients with rheumatoid arthritis, anemias, vague symptoms, and neurological signs, we have an additional 13%. Thus, only 15% of the total group had diseases possibly associated with the lupus diathesis or systemic lupus. The remainder of patients with systemic disease had diseases often to be anticipated in their particular age group and not apparently influenced by the factors causing the biologic false-positive reaction.

To gather further evidence on the probability of systemic disease developing in those patients now apparently well, we analyzed the number of years the serologic test for syphilis had been known to be positive. In the group with systemic disease the patients were known to have had positive reactions, now judged to be biologic false-positive reactions, for from 1 to 40 years, with a mean duration of 4 years. In the group without systemic disease the period of known duration of the positive reaction varied from 6 months to 31 years, with a mean of 2 years. There is a sufficient number of patients with a known long duration of the positive reaction to suggest that this phenomenon may be borne with no apparent detrimental effect in a sizeable group of patients.

However, the high percentage of some abnormal laboratory finding or findings, even in the group with no apparent sign of systemic disease, offers additional evidence that the diagnosis of a biologic false-positive reaction must be given serious consideration. It is yet too early to be able even to give accurate percentages of those who will or will not develop serious disease. At this time we feel that alertness to the findings listed below is indicated.

At the present state of our knowledge certain findings seem to be of significance. The diagnosis of biologic false-positive reaction is of serious significance. It is more common and of more concern in the female. This is often based on the high incidence of systemic lupus erythematosus in the young female. A careful history, examination, and follow-up for vague signs and symptoms of joint pains, unexplained bouts of fever, and easy tiring is mandatory. Additional laboratory studies highly desirable are determination of the sedimentation rate, cephalin-flocculation and thymol-turbidity tests, and complete blood cell counts. If these tests, as well as the history and the physical examination, are normal, then the patient may be observed at yearly intervals, with instructions to return earlier if symptoms appear. If they are positive, more careful and frequent observation is indicated.

Summary

Of 245 patients with persistent biologic false-positive reactions, 23.2% had systemic disease. Females accounted for 71% of the total series and 84% of those with systemic disease. The known onset of the biologic false-positive reaction reached its highest incidence in persons from 20 to 30 years of age. The presence of a biologic false-positive reaction manifested only by a positive Mazzini test is valid. Two per cent of the total series have developed systemic lupus erythematosus. An additional 13% could loosely be classified as having lupus diathesis. One-third of patients with biologic false-positive reaction with no apparent clinical illness were found to have one or more positive laboratory findings indicative of abnormal globulins. The diagnosis of biologic false-positive reaction requires careful history taking and physical examination for vague signs and symptoms, especially in young women. A minimum laboratory examination should include determination of the sedimentation rate, cephalin-flocculation and thymol-turbidity tests, and protein partition.

555 Park Ave. (Dr. Miller).

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CLINICAL NOTES

BRAIN ABSCESS SEVEN YEARS AFTER A POTTS ANASTOMOSIS IN CASE OF TETRALOGY OF FALLOT

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and
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The predilection of patients with tetralogy of Fallot to develop brain abscess is well established. In a review of the literature concerning the association of brain abscess with congenital heart disease, Gluck and co-workers [1] were able to find reports of 20 cases of brain abscess associated with tetralogy of Fallot. Clark and Clarke [2] reported 19 additional cases, in several of which brain abscess was discovered after cardiac surgery. Ingraham and Matson [3] have pointed out that, when focal neurological signs, convulsions, or symptoms of increased intracranial pressure are present in a patient with either tetralogy of Fallot or certain other forms of congenital heart disease, the diagnosis of brain abscess should be considered.

It is important to determine to what extent the surgical procedures now used in patients with tetralogy of Fallot alter the propensity of these patients to develop brain abscess. We wish to report a case in which cerebral abscess developed seven years after a successful Potts anastomosis for tetralogy of Fallot had been performed.

Report of a Case

A 10-year-old girl was admitted to the children's division of the Cook County Hospital with a 10-day history of progressive lethargy, headache, vertigo, and anorexia. The patient had a known congenital heart disease. When she was 3 years old, the diagnosis of tetralogy of Fallot had been established and a Potts anastomosis had been performed. After the operation, there had been marked improvement in her condition. Cyanosis was no longer present at rest, and only mild cyanosis was evident with moderately severe exercise.

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On the patient's admission, physical examination revealed a thin girl who was extremely lethargic and unable to walk. Papilledema was noted in the right eye. Both pupils reacted to light and accommodation. Hemiparesis was present on the left, with some spasticity in the left arm and left leg. The deep reflexes on the left were hyperac ive. Ankle clonus was present on the left. The blood pressure was 110/70 mm. Hg, the pulse rate was 96 per minute, and the temperature was normal. The heart was not enlarged to percussion. A systolic thrill was present at the third and fourth left interspace parasternally. A grade 4 systolic murmur, which transmitted widely, was heard maximally in the same area. A systolic and diastolic murmur, machinery-like in character, transmitted widely and was heard best in the second left interspace parasternally.

Hemoglobin level was 14 Gm. per 100 ml., with red blood cells numbering 4,430,000 per cubic millimeter and white blood cells 16,000 per cubic millimeter, with 68% polymorphonuclear, 2% band cells, and 30% lymphocytes. Urinalysis was negative. The blood culture was sterile. Beta-hemolytic streptococci were isolated from a throat culture. The cerebrospinal fluid, obtained by lumbar puncture, was opalescent, containing many crenated red blood cells. The spinal fluid sugar level was 68 mg. per 100 ml., and protein was 32 mg. per 100 ml. Culture of the spinal fluid was sterile. The Mantoux test was negative. Chest roentgenograms showed that the heart was not enlarged and that the pulmonary vascular markings were normal.

Skull roentgenograms were normal. An electroencephalogram revealed a basic frequency of 2 per second in all leads and occasional slow focal bursts involving all the right-sided leads. The sleep spindles were poorly formed and were absent on the right. There were no seizure discharges. The interpretation of the tracing was that of a grossly abnormal record with generalized slowing and right-sided focal slowing compatible with generalized and right-sided cortical dysfunction.

The patient was treated with daily intramuscular injections of aqueous procaine penicillin. Ten days after the patient's admission, bilateral bur holes were made. With the exploring needle a right parietal brain abscess was encountered and drained of 70 ml. of grey-green purulent material. No organisms were seen on smear, and a culture was sterile. Histological ex-

amination of the membrane of the abscess revealed it to be a pyogenic membrane. The patient made an uneventful recovery after surgery and soon became alert and active. Mild hemiparesis on the left persisted after recovery.

Comment

While it is possible that the cardiovascular anomalies of this patient were not related to the development of the brain abscess, we believe it much more likely that a causal relationship existed between the two conditions. None of the conditions such as infection of the mastoid, infection of the paranasal air sinuses, suppurative bronchopulmonary disease, bacterial endocarditis, or septicemia, which are ordinarily associated with the development of brain abscess in patients who do not have cardiac anomalies, was present in this patient. The known propensity of patients with tetralogy of Fallot who have not undergone surgery to develop brain abscess has been cited.

With regard to the development of brain abscess subsequent to surgery for tetralogy of Fallot, we have been able to find only two reports of such cases. Clark and Clarke [2] reported seven cases of tetralogy of Fallot in which brain abscess was discovered after cardiac surgery. In two of these cases, the brain abscess developed two and three years, respectively, after a successful Blalock anastomosis. In two others, symptoms of brain abscess were present before cardiac surgery but were not recognized. In the remaining three cases, the time interval between the cardiac surgery and the development of brain abscess was so brief that the relation between the two events was not clear. Sweeney and Patton [4] reported the case of an 8-year-old boy who developed a brain abscess three years after a successful Blalock anastomosis. The patient was successfully treated by surgical drainage of the abscess.

Several explanations have been offered to account for the predilection of patients with tetralogy of Fallot to develop brain abscess.[1] It has been suggested that cerebral abscess develops in these patients subsequent to cerebral thrombosis. Polycythemia is usually present in these patients, and presumably their cerebral circulation may be sluggish. For this reason patients with tetralogy of Fallot are subject to cerebral thrombosis, particularly after dehydration. The patient reported in this paper did not have polycythemia nor any indication of sluggish cerebral circulation at the time of onset of her brain abscess.

It is more generally accepted that shunting of venous blood directly into the systemic circulation is causally related to the development of brain abscess.[2] The normal passage of systemic venous blood through the pulmonary vasculature is believed to result in the removal of small septic emboli from the circulation. In tetralogy of Fallot much of the systemic venous blood passes from the right ventricle into the overriding aorta and thence to the brain without first traversing the pulmonary vasculature. While there is increased pulmonary blood flow in the patient who has undergone a successful Potts anastomosis, Blalock anastomosis, or pulmonary valvulotomy, the aorta continues to receive systemic venous blood directly from the right ventricle, and some venous blood continues to reach the brain without immediate previous passage through the pulmonary vasculature.

Before the first case of brain abscess in a patient after operation with tetralogy of Fallot was reported, Maronde,[5] in a discussion of cerebral abscess in congenital heart disease, pointed out that the potentialities for development of cerebral abscess would still be present after operation. It is to be noted, however, that the volume per minute of systemic blood passing to the brain without immediate prior passage through the lungs is less after surgery. Presumably this would decrease the patient's predilection to develop brain abscess but not completely obviate it. It is to be hoped that further study may determine whether the apparent rarity of occurrence of brain abscess in cases of tetralogy of Fallot after surgery is a true indication of extremely low incidence or merely reflects the failure of publication of such cases.

Summary

Seven years after the successful performance of a Potts anastomosis in a 3-year-old patient with tetralogy of Fallot, brain abscess occurred. Because of the persistence, after surgery, of flow of some systemic venous blood to the brain without immediate prior passage through the lungs, the usual operative procedures performed on patients for tetralogy of Fallot do not appear to obviate completely the predilection of these patients to develop brain abscess.

Addendum

Since the completion of this paper, an article has appeared by Campbell [6] reporting five cases of cerebral abscess occurring in persons with tetralogy of Fallot after a successful subclavian pulmonary anastomosis. Of these five cases, four were successfully treated neurosurgically.

840 S. Wood St. (12) (Dr. Rosenthal).

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GASTRIC ACIDITY DETERMINATION PROCEDURES

COMPARISON OF A TUBELESS METHOD WITH AZURE A RESIN COMPOUND AND AN INTUBATION METHOD WITH HISTAMINE

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The purpose of this report is to present a comparison of findings on gastric secretion when a tubeless method with azure A resin compound (Diagnex Improved) and an intubation method with histamine stimulation are both employed in the same patient.

In 1950, Segal, Miller, and Morton [1] described a method for determining the presence or absence of free hydrochloric acid in the stomach without the use of intubation. This procedure consisted of the oral administration of an ion-exchange resin coupled with quinine. Although this technique was reliable,[2] it was not widely adopted because of the complicated laboratory facilities necessary in analyzing the quinine compound excreted in the urine.

The subsequent development of a stable carboxylic resin indicator with azure A for the detection of free gastric hydrochloric acid [3] has provided a method that has proved to be simple and practical. This determination involves a displacement of the azure A of the indicator resin by the hydrogen ions of the free hydrochloric acid of the stomach. The presence or absence of azure A in the urine indicates the presence or absence of free hydrochloric acid in the stomach. Estimation of the amount of azure A excreted is possible by gross visual means not dependent upon special equipment or complex analytical procedures. The carboxylic resin compound with azure A is nontoxic, is not absorbed from the gastrointestinal tract, does not alkalinize the urine or affect the acid-base balance of the body, and does not produce constipation.

Methods and Materials

The subjects of this study were 139 patients, most of whom were ambulatory and attending the gastrointestinal clinic.

Tubeless Method.—The determination by the tubeless method was carried out on fasting patients with an empty urinary bladder. Two capsules or tablets (0.5 Gm.) of caffeine and sodium benzoate were given by mouth with one-half glass of water. A control urine sample was collected one hour later, and the patient was given the granular carboxylic resin indicator with azure A in one-half glass of water. A second urine sample was collected two hours after the ingestion of the dye. Three hours are required for performing the entire procedure. The urine may remain blue for several days, but this has no clinical significance.

The estimation of the quantity of azure A in the urine is performed as follows. The two-hour urine and the one-hour control urine specimens are each diluted with water to approximately 300 ml. If a distinct blue color is observed in the two-hour specimen, the patient has free hydrochloric acid in the stomach and the test is complete. If a definite blue color is not observed, 10-ml. aliquots of the diluted two-hour urine and the one-hour control urine specimens are poured into test tubes and boiled directly over an open flame or placed in a bath of boiling water for 10 minutes. If, after boiling, the diluted two-hour urine specimen develops a blue color, the patient has free gastric hydrochloric acid. If no color develops, the patient has achlorhydria. The boiling procedure changes any colorless conjugated form of azure A that may be present in the urine to free azure A.

Occasionally, after the boiling of the urine, the blue color is doubtful or questionable. When this occurs, the color of the boiled two-hour urine sample as well as of the one-hour control urine sample is compared with known color standards. Only two standards are necessary to determine the presence of free acid or borderline acid secretion. One corresponds to the color intensity of 0.6 mg. of azure A per 300 ml. of solution and the other to the color intensity of 0.3 mg. of azure A per 300 ml. of solution. A reading below 0.3 mg. indicates achlorhydria, and a value between 0.3 and 0.6 mg. is indicative of hypochlorhydria, while values over 0.6 mg. indicate normal acid secretion. If the test cannot be completed on the same day the urine samples are collected, the urine should be acidified and placed in the refrigerator. For acidification, 5 to 8 drops of concentrated (35%) hydrochloric acid should be added to each 100 ml. of urine.

Intubation Method.—The intubation procedure was done as follows. Samples of gastric juice were withdrawn from the stomach of the fasting patient every 15 minutes for a total of 90 minutes. Histamine (0.5 mg.) was given subcutaneously after the 30-minute sample had been obtained. The specimens were titrated in the usual manner, using Töpfer's reagent as an indicator for free acid.

Results

In each of the 139 patients, both tubeless and intubation studies were performed for comparative purposes. In 106 patients (76.3%), the presence of free hydrochloric acid was demonstrated by both the tubeless and the intubation methods. In five patients (3.6%), the tubeless method indicated achlorhydria and the intubation test recorded free acid. In 23 patients (16.5%), the absence of free hydrochloric acid was demonstrated by both methods. Five patients (3.6%), in whom achlorhydria was indicated by the azure A test, showed variable results by the intuba-

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tion test. They appeared to have achlorhydria at one time and to be secreting small amounts of hydrochloric acid at a repeated test, some only after 60 minutes.

Comment

It should be emphasized that in all patients in whom achlorhydria was indicated by the intubation method, the tubeless method likewise indicated an achlorhydria. Also, in every case where the tubeless method indicated the presence of free acid, this was corroborated by intubation with histamine stimulation. Some patients who appeared to have achlorhydria, as indicated by the tubeless method, are either intermittent or late secretors of acid or appear to have hypochlorhydria, as indicated by the intubation method.

The tubeless technique has been adopted with relatively little difficulty. At the time of this report approximately 700 tubeless gastric analyses have been performed at this hospital.

Conclusions

The tubeless method for determining gastric acidity with the use of a carboxylic resin indicator with azure A is a simple test which may be performed on the ambulatory patient. It lends itself readily to use by the practicing physician in his office. When the tubeless method indicates the presence of free acid, this is conclusive. The tubeless technique is useful in detecting patients with achlorhydria. However, in some cases this technique will indicate achlorhydria when the standard intubation test with histamine reveals the presence of acid. Since the tubeless technique is simple and has not failed to corroborate a finding of achlorhydria by the intubation method, it may be useful as a screening procedure to detect achlorhydria in mass surveys for gastric cancer.

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The azure A resin compound used in this study was supplied as Diagnex Improved by E. R. Squibb & Sons, New York, through Dr. Henry Strade.

Technical assistance in this study was given by Virginia Rechnitzer and Pearl Lang.

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NEW VAGINAL HEMOSTATIC RETRACTOR TO REDUCE EPISIOTOMY BLOOD LOSS

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It has been shown by Odell and Seski [1] that a woman may lose, on an average, approximately 253 cc. of blood from an episiotomy wound in the course of a delivery and that this is the chief source of blood loss in most primiparous women. A new vaginal perineal retractor (fig. 1) for use in obstetrics is presented here. Its primary purpose is to prevent loss of blood from the episiotomy or perineal wounds.

It is a broad-bladed retractor with a concave surface, and it is weighted and shaped so as to fit snugly in the episiotomy site and give sufficient compression to the exposed vessels to stop bleeding instantaneously (fig. 2). The handle is angulated away from the anus to avoid any contamination in the handling of the instrument.

This retractor therefore has two main functions. 1. It stops episiotomy blood loss quickly by direct pressure. (It is suggested that two 4-by-4-in. sponges be placed first in the bed of the episiotomy wound and then this weighted retractor placed over them.) 2. It facilitates the repair of a vaginal tear after delivery by keeping the site of the episiotomy dry; therefore, there is no

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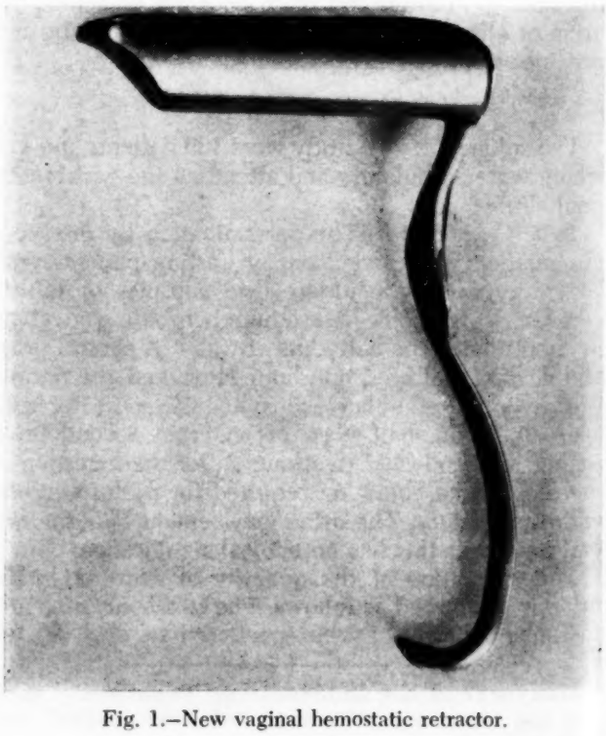

Fig. 1.—New vaginal hemostatic retractor.

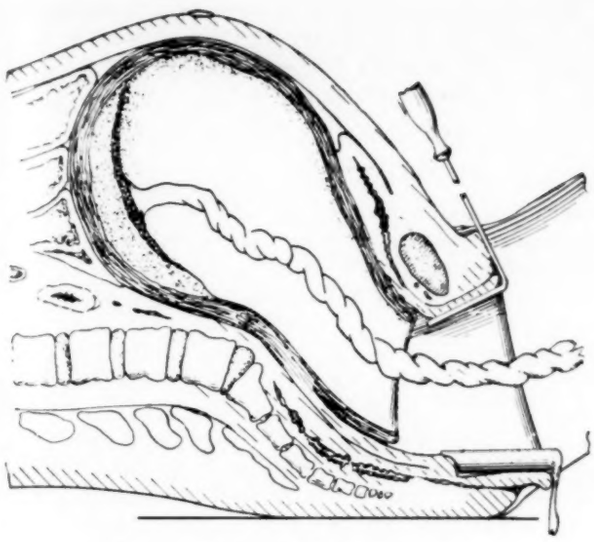

Fig. 2.—Retractor in episiotomy site.

further flooding of blood into the field from the episiotomy. It also aids exposure by retracting the posterior vaginal wall firmly down. Since it is self-retaining, the assistant is freed from holding and pulling down on this retractor and may be of help in other ways.

During the use of this instrument one will readily notice the small amount of blood lost other than that from the uterus. For the mother this saving of blood, which at times can be quite considerable, is always most important, especially from a morbidity and mortality standpoint. This hemostatic retractor has been tested for over two years with complete satisfaction and no ill-effects.

715 W. Sheridan Rd. (13).

The retractor described is manufactured by the Grieshaber Mfg. Co., 4501 W. Armitage, Chicago 39.

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COUNCIL ON DRUGS

Formerly the Council on Pharmacy and Chemistry

Report to the Council

The Council has authorized publication of the following report. Nonproprietary terminology is used for all drugs that are mentioned; when such terminology is not considered to be generally well known, its initial appearance is supplemented by parenthetic insertion of names known to be applied to commercial preparations.

H. D. KAUTZ, M.D., *Secretary.*

CURRENT STATUS OF THE TREATMENT OF RHEUMATOID ARTHRITIS

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Rheumatoid arthritis is a disease involving many connective tissues of the body and manifesting itself as a profound systemic disturbance. Inflammation of the joints and a chronic progressive crippling polyarthritis are only the most obvious manifestations of this process. For many years therapeutic procedures have been based on etiological theories: foci of infection, deranged carbohydrate metabolism, intestinal toxemia, endocrine imbalance, hypersensitivity to various antigens, neuropsychiatric factors, and many others. Treatment directed along etiological theories has so far failed, and we must admit that, as yet, we have discovered no specific etiological agent and no single specific cure. The recent increase in basic research in biochemistry, histochemistry, immunology, and biophysics gives new hope that the pathogenesis of this disease may soon be uncovered.

Temporary Improvement

Many agencies produce temporary improvement in the disease. Artificial fever, anesthetics, starvation, and emotional crises will occasionally be followed by definite improvement; transfusions are, in some instances, followed by a partial remission; pregnancy and nonhemolytic jaundice of sufficient degree produce remissions. In rheumatoid arthritis the immediate and dramatic effects are well known of corticotropin (Acthar, Corticotropin, Depo-Acth) and the glucocorticoids, including cortisone (Cortisone, Cortogen, Cortone) acetate; hydrocortisone (Cortef, Cortril, Hycortole, Hydrocortone); prednisolone (Delta Cortef, Hydeltra, Meticortelone), and prednisone (Deltasone, Deltra, Meticorten). Approximately 90% of patients respond well and usually immediately to these substances. Phenylbutazone (Butazolidin) may produce initial improvement in approximately 40% of patients with rheumatoid arthritis. Remissions also occur spontaneously without identification of a remission agent. Nearly all of these periods of improvement are temporary, and sooner or later the disease activity recurs. We do not entirely understand the mechanism of these remissions, but the very fact that the disease in its early stages is reversible should add not only impetus to the search for the basic mechanism but confidence in ultimate success.

From the Southwestern Clinic and Research Institute.

Long-term Basic Program

Inasmuch as rheumatoid arthritis is a chronic disease and usually a lifetime problem, emphasis should be placed on long-term treatment. Despite the lack of a specific cure, physicians can, with the present knowledge, prevent most of the deformities and sufficiently modify the disease to restore a majority of these patients to useful lives. Under inadequate treatment, patients with rheumatoid arthritis will continue to develop progressive crippling deformities and joint destruction. When a specific cure is discovered, it will not correct deformities or restore joints already destroyed. It is therefore essential, in the long-term management of this disease, to place every patient on a basic program directed toward the individual as well as his disease. Such a basic program should include at least the following eight items: psychological adjustment, a balance between rest and activity, diet and bowel management, correction of anemia, cautious removal of foci, relief of pain, corrective and postural exercises, and prevention and correction of deformity.

Psychological adjustment is essential for every patient. He must be told quite frankly what is known and what is not known about his disease. Failure to properly orient a patient to the long-term problems of rheumatoid arthritis is largely responsible for the fact that there are thousands who seek quick cures and quack remedies. Adjustments to family, business, and economic factors are essential. The patient must be taught to think in terms of months and years, not weeks. A very fine balance between knowledge of the facts and hope for the future needs to be achieved. No treatment of this disease will be successful over a prolonged period without this preparation.

Rest and activity should be carefully balanced on the basis of fatigability and pain. Moderate activity is helpful, provided the patient is not attempting to walk on bent and painful joints and provided the activity is followed by adequate rest.

Diet and bowel management must be prescribed accurately by the physician. This is essential, not because there are special diets that will cure arthritis but because the physician must make certain that the patient is on a highly nutritious, well-balanced diet; unless one is prescribed for him, he will most certainly, sooner or later, embark on one of the fad diets.

Correction of anemia in rheumatoid arthritis is often difficult, and simple iron preparations usually fail to help. A trial of one of the iron preparations is sometimes effective, though gastric irritation is often a problem. It is doubtful that liver, cyanocobalamin (Vitamin B_{12}), or other injections materially alter the anemia. When the disease is early and acute, three or four small fresh blood transfusions given at weekly intervals not only may help correct the anemia but often will give temporary improvement in the arthritis.

Removal of foci of infection should be undertaken not with the idea of curing the disease but only for improvement of general health. It is well to approach foci removal in rheumatoid arthritis with caution, as not infrequently an acute exacerbation may follow such a removal. Prophylactic antibiotic therapy and, in acute cases, a blood transfusion are worth doing before removal of a definite focus.

Relief of pain is usually accomplished by adequate rest; splinting or supports for the acutely affected joints; gentle warmth, but not baking; and aspirin or one of the other salicylates in adequate amounts. If opiates are required, the diagnosis should be reconsidered.

Corrective and postural exercises should be taught carefully and carried out faithfully, because for the ambulatory patient, as well as for the bed patient, they offer the best insurance of maintaining motion and improving muscle tone, thus preserving joint and muscle function.

Prevention and correction of deformities are essential in every patient with rheumatoid arthritis. The probability of flexion contraction and residual deformity should be anticipated and prevented. Much has been written on this subject, and every physician who accepts responsibility for treating even one patient with rheumatoid arthritis must be alert to this aspect of the management of this problem. Deformities can now be largely prevented and very many corrected after they occur. Knee flexion contractions in patients who now fill the wheelchairs can be prevented 100%. Prevention of deformities is simple and easily accomplished. Their correction is much more difficult and time-consuming.

Elective Measures

Once the patient is established on a full basic program, the physician is then free to choose from among the several elective procedures or measures, such as transfusions; administration of gold salts; change of climate; x-ray therapy; pregnancy; administration of gluco-corticoids, including cortisone, hydrocortisone, prednisolone, and prednisone; and administration of corticotropin (ACTH), phenylbutazone, and experimental anti-inflammatory agents.

Transfusions.—Patients with acute early rheumatoid arthritis often respond well and occasionally dramatically to repeated transfusions of ordinary fresh blood. Usually 250 to 300 cc. given weekly for three to five weeks is the method of choice. Transfusions are not advised for the management of the chronic stage of the disease.

Gold Therapy.—Despite more than 25 years of experience with gold salts in the treatment of rheumatoid arthritis, some differences of opinion still remain among students of the disease as to the value of gold therapy. We believe that gold is still the elective agent of choice in properly selected cases. In early active peripheral rheumatoid arthritis with minimal joint destruction and in the palindromic phase of rheumatoid arthritis, it offers the best chance of a very long and satisfactory remission. We regard palindromic rheumatism as an atypical rheumatoid arthritis. Gold therapy is seldom worth using in the far-advanced disease with much joint destruction and very little inflammatory reaction remaining. Although toxic effects may occur, we believe that with adequate precautions they are less frequent and less serious than those encountered in long-term therapy with gluco-corticoids. Should toxic manifestations occur with gold therapy, corticotropin appears to be a specific for the skin manifestations and of value in other toxic effects. It is far easier and safer to use than dimercaprol (BAL),

one of the helpful antidotes for gold toxicity. If the disease is acute, we frequently use minute doses of purified corticotropin (10 units of the gel given subcutaneously) three times weekly during the first few months of gold therapy and have no difficulty discontinuing its use when the gold remission occurs. Some temporary relief persists from this minute amount for 12 to 24 hours. When gold is used properly in selected early cases, effective remissions are secured by this routine in a very worthwhile percentage of cases. Another point to be borne in mind is that once a remission has occurred, usually after three to five months, gold therapy is not discontinued, but maintenance dosages are administered at longer intervals for years.

Climate.—A small percentage of patients with rheumatoid arthritis experience definite improvement with a change to a dry, warm climate. The chance that climate may help does not warrant disruption of a family's economic security, as climate is no panacea for rheumatism and certainly not a cure for rheumatoid arthritis. Climate is also no substitute for careful medical supervision. Most patients with rheumatoid arthritis are more comfortable and more easily cared for in a suitable climate, but a minimum of three to six months is required for a trial.

X-ray Therapy.—Therapy with x-ray is not helpful in peripheral rheumatoid arthritis, but it is one of the valuable aids in rheumatoid spondylitis.

Pregnancy.—In a very high percentage of patients with rheumatoid arthritis, pregnancy results in excellent remissions. However, the remission lasts only for the term of the pregnancy.

Gluco-corticoids (Corticosteroids).—It is now generally agreed that the effects of the gluco-corticoids are only suppressive and do not alter the underlying disease mechanism. Moreover, joint destruction may continue to advance even during excellent clinical remissions. Neither intermittent courses of treatment with these substances nor continuous administration of effective suppressive doses has resulted in very encouraging results in long-term therapy. In our four-year control study of 36 patients with early active rheumatoid arthritis who were treated with maximum safe suppressive doses of cortisone, 33 patients achieved a grade 1 or grade 2 remission initially. After two years only two patients maintained this degree of improvement, and at the end of four years no patient remained in grade 1 or grade 2. Only two patients were receiving enough benefit to remain on therapy with the medicaments after four years. In a group of 60 patients with less active disease and advanced joint changes who were selected primarily for rehabilitation, the results of minimal doses of cortisone appeared to be very worthwhile. Cortisone acetate was administered orally in doses of 50 mg. per day or less, with no attempt at suppressing the disease, but only in an attempt to assist rehabilitation. Of these 60 patients, 26, or nearly half, were still being materially helped at the end of four years.

Hydrocortisone is a more potent anti-inflammatory agent than is cortisone, but the unfavorable physiological effects are qualitatively the same. In the systemic treatment of rheumatoid arthritis, its advantages over cortisone are not impressive. Hydrocortisone acetate, employed as a local anti-inflammatory agent, is given to selected patients by intra-articular injection, with definite help.

Prednisone and prednisolone, even more powerful anti-inflammatory agents, do not significantly disturb electrolyte and water balance as do cortisone and hydrocortisone. However, in our experience, long-term therapy with these drugs is no more successful than with cortisone. These substances produce marked adrenal suppression, frequently lasting for several weeks after withdrawal of the drug. The risk of peptic ulcer (often silent with perforation), disturbed glucose metabolism, and the tendency to capillary bleeding are increased with administration of these substances as compared to cortisone. Minimal doses of 5 to 7.5 mg. daily of prednisone and prednisolone are often very helpful in rehabilitation, though even with this dosage unfavorable physiological effects may occur.

When one considers the frequency of unfavorable physiological effects associated with long-term gluco-corticoid therapy, together with the high failure rate experienced, it should be clear that only after careful selection of patients and for special reasons should the gluco-corticoids be used in early active rheumatoid arthritis. Although our experience with juvenile rheumatoid arthritis is not extensive, it appears that children tolerate long-term gluco-corticoid therapy better than do adults. A number of reports by other investigators express a similar opinion.

Corticotropin.—The results of our four-year study in which continuous suppressive doses of corticotropin were given for the treatment of rheumatoid arthritis are quite similar to those achieved with cortisone and show the same high failure rate. Corticotropin is of value in restoring adrenal function when suppression has occurred with the use of gluco-corticoids, especially when discontinuance of their use becomes necessary.

Phenylbutazone.—The initial response of patients with peripheral rheumatoid arthritis to phenylbutazone is not as dramatic as that to the gluco-corticoids or corticotropin, nor does as favorable a response occur in so high a percentage of patients. In our experience, approximately 40% of the patients with peripheral rheumatoid arthritis achieve an initial worthwhile improvement, but a relatively small number of these reach a grade 1 or grade 2 remission. However, once patients attain a worthwhile improvement without significant toxic effects, the failure rate is not so rapid as with gluco-corticoids and corticotropin therapy. Adverse physiological effects occur and require constant vigilance. These may include edema, hypertension, rashes, symptoms of peptic ulcer, and lowered hemoglobin levels. Blood dyscrasias and hepatitis have also been reported. Daily dosage in excess of 0.4 Gm. is not likely to be more effective than smaller doses, and the risk increases with the larger doses. In peripheral rheumatoid arthritis, phenylbutazone is best reserved for the occasional case which does not respond to other measures and which does show a favorable response within 10 days to relatively small doses. Most toxic manifestations, though not all, occur during the first three months of treatment. Despite the limitations of phenylbutazone in the treatment of peripheral rheumatoid arthritis, it is an extremely useful and effective

agent in rheumatoid spondylitis. Our studies show that 89% of patients with rheumatoid spondylitis, without peripheral involvement, responded rather dramatically to initial administration of no more than 0.2 Gm. of phenylbutazone daily. Forty-eight such patients who responded well initially, without toxic effects, have now been followed for more than four years. Of this group, 44 are still doing remarkably well. Of the four patients removed from treatment, one developed a bleeding peptic ulcer and one hematuria with recurrent urinary calculi; the drug was no longer effective in two of the patients. This represents an extremely low failure rate. We have withheld x-ray therapy from the patients with rheumatoid spondylitis who are doing well on this routine because the results, so far, are superior to those achieved with x-ray therapy.

Other Experimental Anti-inflammatory Agents.—Several new synthetic gluco-corticoids are now being investigated, and it is certainly possible to increase several fold the anti-inflammatory effects by altering the structure of the molecule. The problem is to achieve this without also multiplying some of the undesirable physiological effects that occur. Inasmuch as prolonged treatment is essential to the management of this disease, evaluation of these newer steroids from the long-term viewpoint is obviously impossible at this time. Search for a synthetic steroid with only anti-inflammatory action is being continued, but at this writing such a compound which is entirely free of undesirable physiological side-effects has not been reported. Postpartum and placental serum, primaquine phosphate, quinacrine (Atabrine) hydrochloride, chloroquine (Aralen) phosphate, nitrogen mustards, aminopterin sodium, procaine hydrochloride given intravenously, para-aminobenzoic acid, adenosine triphosphate, heparin sodium, and others previously have been reported to show favorable therapeutic effects in rheumatoid arthritis. However, they have been largely abandoned for this purpose either because of excessive toxicity or failure to maintain what appeared to be early improvement. In several very recent reports chloroquine has again been described as a useful drug.

Comment

The present trend in treatment of rheumatoid arthritis is to emphasize a complete and carefully planned basic program, which should embrace at least the eight fundamental items discussed previously. Aspirin, or one of the other salicylates, is considered to be the safest and most desirable of the drugs used for relief of pain. Of the elective procedures, gold therapy administered in early active disease, when successful, often induces long and quite satisfactory remissions. Gluco-corticoids, given in minimal doses, are extremely valuable in rehabilitation and in special situations in which the disease is older and much less active. Corticotropin may be used in the same fashion, with minimal doses given every other day. Small doses of phenylbutazone, administered under careful supervision, are effective in the control of rheumatoid spondylitis and show a low failure rate in this form of the disease.

In view of the rapid failure rate, the unfavorable physiological effects, and the progression of joint destruction, all of which are associated with long-term therapy, we believe that the gluco-corticoids have only a very limited place in the treatment of early active rheumatoid arthritis. Furthermore, the psychological impact of the early dramatic improvement followed by gradual failure and relapse as the months go by is indeed an emotional disaster for the patient and often a cause of referral by the physician. Some excellent studies have shown that the five-year results with cortisone are no better than those with aspirin. However, these statistics are not quite fair, because they do not take into account the total working days during the period. There are occasions when, with a full understanding between patient and physician, it is advisable or necessary to secure maximum physical activity over a given short period of time, and this can often be accomplished with the gluco-corticoids. It is essential that the cost to the future of buying this time must be carefully evaluated and understood by the patient as well as the physician. It is only fair to state that honest differences of opinion exist, regarding the role of gluco-corticoids in the treatment of rheumatoid arthritis. The conclusions expressed in this report, while shared by many, would be thought too pessimistic by some and too optimistic by others.

Finally, if the physician will spend sufficient time and effort to establish his patient on a sound basic program and only then, if necessary, select elective measures best suited to the individual problem, the results of treatment will be surprisingly rewarding.

Addison's Disease and Active Tuberculosis.—Clinical and laboratory methods for establishing the cause of adrenal insufficiency have been found to have many limitations. The most useful of these findings are adrenal calcification, which is suggestive of a tuberculous etiology, and nonreactivity to tuberculin, which is suggestive of idiopathic adrenal atrophy. Hormonal replacement therapy for adrenal insufficiency is essential for the management of Addison's disease with or without active tuberculosis. . . . . Active tuberculosis in the presence of adrenal insufficiency shows tendencies toward chronicity and relapse similar to those which characterize tuberculosis in persons without Addison's disease. Antituberculous therapy should be based on the same medical and surgical principles which are applicable to individuals who do not have concomitant adrenal insufficiency. In a patient with known adrenal insufficiency, the appearance of increased symptoms, increased hormonal requirements, tachycardia, fever, leukocytosis with a relative lymphopenia, and an elevated erythrocyte sedimentation rate should suggest the presence of either active tuberculosis or some similar chronic infection.—J. P. Sanford and C. B. Favour, The Interrelationships Between Addison's Disease and Active Tuberculosis: A Review of 125 Cases of Addison's Disease, *Annals of Internal Medicine*, July, 1956.

COUNCIL ON FOODS AND NUTRITION

Report to the Council

The Council has authorized publication of the following report. The Council is pleased to acknowledge the co-sponsorship of this article by The Nutrition Foundation, Inc.

PHILIP L. WHITE, SC.D., *Secretary.*

ESTROGEN RESIDUES IN MEAT—PUBLIC HEALTH ASPECTS

George M. Briggs, Ph.D., Bethesda, Md.

An important recent development in the food-producing industry is the administration of compounds with estrogenic activity to beef cattle and poultry to improve growth and feed efficiency. The practice is especially prevalent today in the beef cattle industry; it is estimated that several million beef cattle each year, or about two-thirds of all cattle in feed lots in the United States, are being treated with estrogen-active compounds. In addition, many millions of chickens and turkeys are being treated annually.

The widespread use of estrogens in livestock raising is largely a result of the established benefits: reported increases of as much as 20% in weight (averaging about 12%), earlier marketing, an average of about 10% saving in feed, and, often, improved carcass quality.[1] Although the practice of "hormonizing" beef cattle started as recently as November, 1954, it is now firmly established and is understandably popular with feedmen. It is to be expected that the practice will spread to other age groups of cattle and perhaps to other species of animals, as evidenced by the Food and Drug Administration's approval in August, 1956, of the use of diethylstilbestrol in the ration of young beef calves just starting on grain.

Since estrogens can be dangerous when used improperly, the use of estrogens in animal production presents certain public health problems. From the public health aspect, the following questions need to be answered. 1. Do residual amounts of compounds with estrogen activity remain in meat and poultry? 2. If so, is there danger to man in the consumption of such residues? 3. What other hazards to the public exist from the practice, such as accidental contamination of feed-mill personnel and farmers, contamination of soil and water, and accidental contamination of foods intended for human use?

Estrogens Used

It is important to review briefly the present status of estrogens used in fattening animals. Diethylstilbestrol and estradiol are the only compounds with estrogen activity that are approved by the FDA for use in beef cattle at the present time. Diethylstilbestrol, most commonly used for this purpose, is available by chemical synthesis and is widely used as a therapeutic agent.[2] The artificial estrogens have the advantage of being active when given orally and are less expensive than the natural estrogens. The chemical relationship of diethylstilbestrol to the naturally occurring estrogens (estrone, estradiol, and estriol) is shown in figure 1. In general, diethylstilbestrol and the natural estrogens may be considered reasonably similar in terms of biological effects and possible toxicity.[2]

A patent has been granted to the Iowa State College Research Foundation, Inc., for the use of diethylstilbestrol in the feeding of beef cattle. The foundation, in turn, licenses manufacturers who distribute premixes containing 10 Gm. of diethylstilbestrol per pound to approved feed manufacturers under close state and federal supervision. The premix is not available to individual farmers. Two pounds of a feed supplement made from the premix and containing 10 mg. of diethylstilbestrol per 2 lb. are used in the feed of beef cattle each day during the growing and fattening period. Ear implants of diethylstilbestrol are also available for use in the beef cattle industry. This latter method of administration has the advantage of requiring considerably less diethylstilbestrol to produce similar results.

In poultry, diethylstilbestrol implantations have been used for "chemical caponization" since 1947, although the practice is not as widespread relatively as in the beef cattle industry. A pellet containing 12 mg. of diethylstilbestrol is implanted at the base of the head about four to six weeks before the bird is marketed. Another synthetic compound, dienestrol diacetate, closely related to diethylstilbestrol, was approved in 1954 for oral use in poultry.[1]

Approval by the FDA has been granted recently for the implantation of pellets containing estradiol and progesterone (natural hormones) in both beef cattle and lambs. The pellets are available to farmers through veterinarians. Although a number of studies of diethylstilbestrol feeding of lambs and swine have been made, the results have not been particularly promising, and approval for the use of this compound in these animals has not been given by the FDA.

Residues in Poultry Tissues

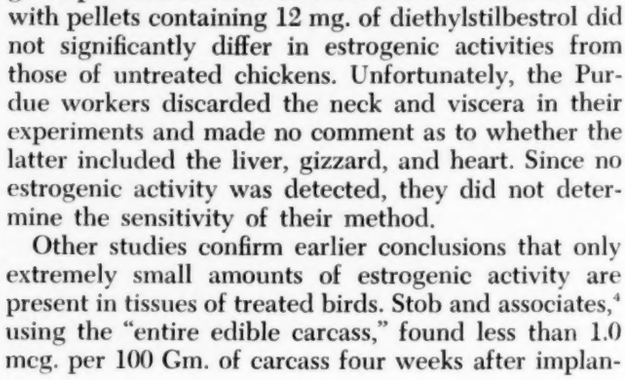
The earliest studies on estrogenic residues in meat were made with poultry. From these studies [1a] it was concluded that tissues of birds treated with either

From the Laboratory of Nutrition and Endocrinology, National Institutes of Health, Public Health Service, United States Department of Health, Education, and Welfare.

diethylstilbestrol or dienestrol diacetate contained not over 1.4 mcg. of activity per 100 Gm. of carcass, including the liver and skin. This amount may be considered negligible.

More recently, Merker and co-workers [3] of Purdue University have used improved methods of extraction and biological testing for estrogenic residues in poultry. In 1955 they reported that the free and conjugated phenolic residues obtained from chickens treated with pellets containing 12 mg. of diethylstilbestrol did not significantly differ in estrogenic activities from those of untreated chickens. Unfortunately, the Purdue workers discarded the neck and viscera in their experiments and made no comment as to whether the latter included the liver, gizzard, and heart. Since no estrogenic activity was detected, they did not determine the sensitivity of their method.

Other studies confirm earlier conclusions that only extremely small amounts of estrogenic activity are present in tissues of treated birds. Stob and associates,[4] using the "entire edible carcass," found less than 1.0 mcg. per 100 Gm. of carcass four weeks after implantation of a diethylstilbestrol pellet. Trace amounts of estrogenic activity were found by Swift [5] in tissues of birds treated with diethylstilbestrol. "No detectable estrogen" was found in edible tissues of birds fed dienestrol diacetate by Tiger, Mitchell, and Goff,[1b] who used a rat assay that is usually considered less sensitive than the assay based on the weight of the mouse uterus.



Residues in Beef Cattle Tissues

Only in the past three years have studies been reported on the estrogenic activity of tissues of beef cattle treated with diethylstilbestrol. In all cases, results have shown extremely low or negligible estrogenic residues in tissues. Since these studies have not been previously reviewed, the reports are summarized briefly.

The first study of estrogen residues in tissues of beef cattle appears to be that of Stob and associates [4] in 1954. Using uterine weight changes in ovariectomized mice, these workers demonstrated the presence of approximately 1 mcg. or less of estrogenic activity per 100 Gm. of muscle and liver in beef cattle implanted with a pellet containing 120 mg. of diethylstilbestrol. A more recent report from the same laboratory [6] concluded that "no residual hormone" could be detected in the meat of steers fed 10 mg. per day of various estrogens as compared with control animals. This was true whether or not the feeding of hormones was discontinued one or seven days before slaughtering. Swift,[5] in 1954, using a less sensitive chemical assay, could not find estrogenic residues in tissues of treated steers.

Results of additional work at a number of institutions were reported in 1956. Carefully controlled experiments conducted at the Iowa Agricultural Experiment Station by Preston and co-workers [7] showed that "no detectable estrogenic residues" could be found in samples of lean meat, fat, liver, heart, and kidney tissues, or in the pooled offal organs (tripe, intestine, lungs, and spleen) of beef cattle fed 3 to 12 mg. of diethylstilbestrol per day, in some cases up to the time of slaughter. The authors used two sensitive assay techniques based on the weight response of the mouse uterus, with which as little as 0.2 mcg. of diethylstilbestrol per 100 Gm. of meat can be detected.

Turner [8] has determined the estrogenic activity of a number of tissues from beef cattle fed 10 mg. of diethylstilbestrol per day. In his test, the diethylstilbestrol was removed from the ration about 44 hours prior to slaughter. Pooled samples of tissues, taken from 20 treated animals and 10 control animals, were frozen and tested in ovariectomized mice in an assay that was sensitive to 0.2 mcg. of diethylstilbestrol per 100 Gm. of tissue. The tissues chosen for assay included those most likely to contain estrogenic activity, such as the liver, kidney, lungs, spleen, portions of the digestive tract, depot fats, and blood, as well as samples of edible red meat. The results showed no detectable residues in any of the tissues examined, with the possible exception of the kidney (0.4 mcg. per 100 Gm.) and the lungs (1.0 to 1.2 mcg. per 100 Gm.).

Considerable estrogenic activity was reported by Turner [8] to be present in the feces of cattle which were fed estrogen (stated to be as high as 1 mg. per 100 Gm.). Byerly [1b] states that "feces of stilbestrol-fed steers do have estrogenic activity" but at present "provide no cause for alarm." Obviously, this aspect of the practice of estrogen feeding deserves additional study.

Further studies with estrogen residues in tissues of cattle were made by Stob and associates in 1956.[9] Contrary to their earlier studies, "residual" amounts of estrogenic activity were found in the meat, kidney, liver, and intestines of cattle receiving 10 mg. of diethylstilbestrol per day up to the time of slaughter.

Gossett, Smith, and Downing [1b] have measured estrogenic residues in the tissues of steers fed as much as 200 mg. of diethylstilbestrol per day, 20 times the usual level, over periods ranging from 28 to 104 days. Using a sensitive mouse assay, they reported "no

estrogenic residues" in the lean meat or fat when the hormone was removed from the feed 12 to 48 hours before slaughter. However, "trace" amounts, up to 5 mcg. per 100 Gm. of tissue, were found in the liver, kidney, and tripe of cattle fed 200 mg. of hormone per day up to 12 hours before slaughter. When the hormone was removed 48 hours before slaughter, the amounts in these organs were less than 1 mcg. per 100 Gm. of fresh tissue. Up to 1 mcg. of estrogen activity was found per 100 Gm. of liver, tripe, and kidney in steers fed 10 mg. of diethylstilbestrol for 28 days and up to 12 hours before slaughter.

Only negligible amounts of estrogenic activity have been found in tissues of swine [10] and sheep [11] given various levels of diethylstilbestrol. Since the FDA has not released the use of diethylstilbestrol for feeding swine and sheep, this aspect of the problem is not discussed further.

Public Health Aspects

In answer to the question of whether residual amounts of compounds with estrogenic activity remain in meat and poultry, it must be concluded from the facts reviewed that trace amounts of estrogen activity may sometimes be found by sensitive assay methods in meat from beef cattle and poultry treated with the usual levels of compounds having estrogenic activity. Since such compounds are not destroyed by cooking, it is possible that a person eating large amounts of liver, kidney, or other organs from animals treated with estrogen could consume up to several micrograms of compounds with estrogenic activity per day. However, based on the average daily consumption of meat, less than 1 mcg. of compounds with estrogenic activity would be consumed.

The next question that must be answered, therefore, is, "Are these extremely small amounts of compounds with estrogenic activity safe for human consumption?" This question must be answered affirmatively in the light of present knowledge when one considers the following facts:

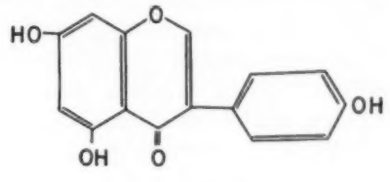
1. Much larger amounts of estrogens are synthesized by men and women each day, circulated in the blood stream,[12] and metabolized [2] or excreted in the bile or urine.[13] In women, milligram quantities are synthesized daily during the later stages of pregnancy and in certain stages of the menstrual cycle.

2. Animals and humans consume foods containing compounds with estrogenic activity under normal conditions.[14] As stated by Luther,[1b] for instance, tissues from normal (untreated) steers contain up to 0.4 mcg. of compounds with estrogen activity per 100 Gm. Gassner [1b] also found estrogenic activity in tissues from untreated steers. Milk from untreated dairy cows may contain up to 0.8 mcg. of estrogens per 100 Gm. of dried milk, although such values would be expected only during the latter part of the gestation period. Also, normal foods of plant origin, such as lettuce, alfalfa, clover, wheat, oats, and corn, may contain appreciable amounts of compounds with low estrogenic activity.[14] One such natural compound with low estrogenic activity is genistein, an isoflavone found in relatively large amounts in clover, soybean meal, and elsewhere (fig. 2).

3. Since the 1930's, countless thousands of men and women have been treated with therapeutic doses of artificial and natural estrogens ranging from 1 to 10 mg. per day (up to 400 mg. in exceptional cases) with no permanent detrimental after-effects.[15] Also, estrogens have been used in certain cosmetics resulting in the absorption of trace amounts of estrogens by thousands of women.

Although it is a fact that estrogens are normally present in foods and that they are used therapeutically, it is recognized that this does not prove unequivocally that the residues in meat are safe for human consumption. However, when considered with point 1, stated previously, the facts certainly are more than sufficient to justify the present conclusion that estrogen residues in meat are safe.

Despite the abundance of evidence showing the safety of small tissue residues of estrogens, it has been suggested by Knight and co-workers,[1b] by Hueper,[16] and by statements in the lay press that man's consumption of meat from animals treated with estrogen



GENISTEIN

presents a hazard because of a known causal relationship between certain experimental animal cancers and estrogens.[17] However, at the present time there is absolutely no evidence that the extremely small amounts of estrogen residues, or degradation products, that might be consumed would have any effect on cancer in either man or experimental animals. Also, evidence is lacking that even much higher levels of estrogens administered to humans may be a direct cause of cancer.[17] Thus, as pointed out by Hines, Berganstal, and Gassner,[1b] the negligible amount of estrogen activity in meat from animals treated in the usual manner presents no cancer hazard to man as far as can be determined from present knowledge. It would seem desirable to continue research in this field as a precautionary measure, however.

It is true that certain health hazards to man do exist from the general practice of administering estrogens to animals. Contamination of personnel in estrogen-manufacturing plants has occurred,[14a] and it would seem that, without proper care, feed-mill personnel and even farmers could become contaminated. Also, mistakes in mixing animal rations can occur. An example has been reported [18] in which contamination of commercial mouse diet with estrogens results in a cessation of breeding in a mouse colony and in a large

loss of valuable animals. Contamination of soil with estrogens may occur in a feed lot or wherever litter or manure is discarded, but further research is needed on this point. It is also possible that unabsorbed portions of estrogen pellets implanted under the skin of animals could be present in meat when used as food for animals or man.[1] All of these hazards are admittedly possible but at present are being controlled or prevented as far as humanly possible by strict control of estrogen production, distribution of estrogen premixes to feed manufacturers, and removal of estrogen from feed before slaughter.[1b] Careful attention is also being given by feed manufacturers and farmers to estrogen inventories and to mixing, labeling, injecting, and feeding as outlined by the FDA and others.[1b] With such care there can be no actual danger to the consumer of food products from animals treated with estrogen, thus making available a new and important tool for the production of more and better food. (Briggs and Gay, and Scoville [1b]).

Summary

Administration of compounds with estrogenic activity to beef cattle and poultry to improve weight gains and feed efficiency has become a widespread practice in animal husbandry in this country. Meat produced from these animals contains a negligible amount of estrogen activity, supplying from 0 to 1 mcg. of estrogen per day in the human diet. This amount presents no hazard to man, since it is considerably less than that normally present in the body and much less than the therapeutic dose. The amount of estrogenic activity is no greater than that in an ordinary diet containing milk, leafy vegetables, cereals, and meat or organs from untreated animals.

The potential hazard of the practice of estrogen administration to animals lies in the possible exposure of personnel in manufacturing plants and in the results of mistakes in mixing and feeding. These hazards, however, can be carefully controlled, and, with the continued vigilance of feed manufacturers, state feed control officials, and the FDA, the use of estrogens in animal production provides an important tool for improved efficiency in food production.

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MEDICINE AT WORK

MEDICINE'S BIGGEST BATTLE: TAMING TIME

AIM IS NOT MERELY TO PROLONG MAN'S LIFE SPAN, BUT TO KEEP HIM ACTIVE

In Anaheim, Calif., not long ago Peter V. Ortiz, 106, opened a bank account to start saving for his old age. Bert Rhoads celebrated his 85th birthday by walking up—and down—898 steps of the Washington Monument. And in Detroit, Henry Shaw, 95, though crippled and receiving only $85 a month, gave $25 to the Torch Fund, saying, "I want the kids to have it."

These little happenings, recorded in the nation's news columns, illustrate a persistent optimism in our aging population. It is an optimism that goes beyond the bright remark, the big show, the human interest pitch. More in seriousness than in jest, so-called old age for an increasing number of citizens is becoming a delightful time of life when you can whistle while you wash your teeth. The delight, however, is in whistling, not washing. And here is where medicine faces its greatest challenge: to help bring growth, motivation, and fulfillment to a larger majority of the population. Longer life, in itself, is not enough.

With the population of Americans over 65 increasing at twice the rate of our over-all population rise, it has been apparent to leading gerontologists that we no longer have the choice of dying young or living into ripe old age. Never have the ranks of "old timers" been so crowded and unexclusive—14,500,000 of them aged 65 or older, or 8½% of the U. S. population (with an estimate of 25 million by 1982). Yet, today, while suddenly finding themselves surviving as "fittest," a substantial number of them are spending their last years with a variety of disabilities.

The magnitude of the situation is best described by Dr. David B. Allman, President of the American Medical Association: "The most important single problem facing the medical profession today is the care of the aged. Medicine is largely responsible for the increasing number of people over 65, so we must solve the medical and help solve the economic problems which result."

How is medical science meeting the challenge? It is closing ranks—among specialty groups, pharmaceutical laboratories, educators, public health resources, and hospital research—to attack every phase of this problem. In concepts of nutrition, exercise, mental health, recreation, and rehabilitation advances are steadily being made.

In California, the Alameda–Contra Costa County Medical Association sets up classes for relatives of disabled elderly patients who thus are able to benefit by proper care in a secure home environment instead of in a less personal institution (where cost of care is 10 times as much as in the home). The State Medical Society of Pennsylvania devises a postemployment, preretirement plan for financing premiums for continued Blue Cross and Blue Shield. Wisconsin state medical society members gather for sessions on medical, social, and economic problems of the aged. The Philadelphia County Medical Society helps raise standards in custodial homes, joins in organizing a geriatrics division at Rush Hospital, sponsors a symposium on aging, and coins the word "Gericrafters" for delighted oldsters who are working with the doctors in developing various skills and crafts. And in New York City's day centers, a recreation program described also as "a mental health program" has men and women in their 80's eagerly playing in orchestras, studying algebra, and painting city scenes.

A. M. A. Efforts

At the national level, meanwhile, medical societies are taking part in an intensified A. M. A. campaign begun 40 years ago to urge periodic physical examinations for all Americans by their family physicians. By this effort, doctors hope to find the very abnormalities which might be corrected if caught early—but which disable a person in advanced years if detected too late or not at all.

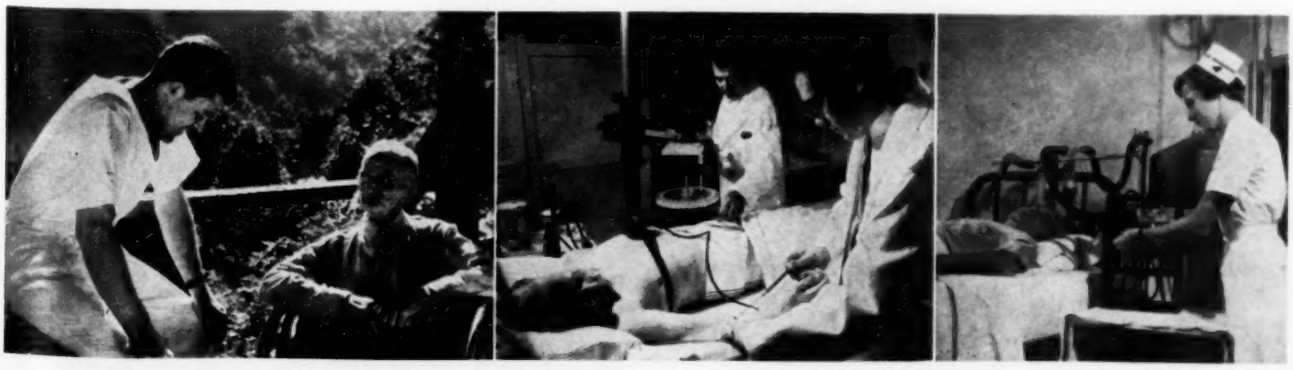

Fig. 1.—*Left,* illustrating the key role of family physicians in helping solve problems of the aging, Dr. George Bond interviews an elderly patient. *Center,* doctor at right is using a dye solution procedure to determine cardiac output in study of aging. *Right,* staff nurse performs a routine test to determine the relationship of aging to the basal metabolism rate. (Photos from National Institutes of Health, Public Health Service.)

There is hardly a phase of A. M. A. activities which does not aim at solving some geriatric problem. The Bureau of Health Education is keeping alive public interest in the topic with pamphlets, articles in *Today's Health*, and sound recordings for radio stations across the land. The Council on Foods and Nutrition is studying and reporting on diet and dietary supplements for the aged. The Council on Drugs is helping evaluate the many substances which pharmaceutical firms and allied research laboratories are developing for the diverse medical needs of our older population. This week, the Council on Rural Health is launching a cooperative effort with 4-H Clubs, agricultural extension groups, and farm and grange organizations to utilize the wisdom of retired people in rural areas by enlisting their services as instructors, advisors, and consultants for future farmers and ranchers. The Council on Medical Education and Hospitals is gathering data on the integration of geriatrics (as one of a number of essential subjects) in medical school curriculums. The Council on Industrial Health is handling correspondence on the controversial question of when an employee reaches proper retirement age. The Council on Mental Health is keeping track of appropriate developments in that field. An intra-A. M. A. committee representing five councils is exploring efforts to rehabilitate the disabled elderly. THE JOURNAL, reflecting these other developments, is supplementing its regular scientific reports on aging with publication this fall of a special series of 15 original articles covering various aspects of the subject.

But the A. M. A. group most closely concerned with the over-all situation is the two-year-old Committee on Aging, headed by Dr. Henry B. Mulholland of Charlottesville, Va. One big objective of this vigorous seven-man group is to impress upon the practicing physician the important role he can play by assuming community leadership to enrich the lives of older citizens. Soon the A. M. A. committee will publish guides for state and county medical societies, to help them organize with allied medical and lay groups in meeting specific needs of the aging in their own areas. "The aging problem is primarily a community responsibility," says Dr. Mulholland. "There is an emphatic need for careful community planning and for coordination of various agencies and facilities."

Community Coordination

"Community" and "coordination"—these two words stand out wherever there is a concerted attack on problems of the aging. The A. M. A. committee makes a point of scheduling its sessions with allied health and nonmedical groups in a different part of the nation (Seattle last fall, Dallas this spring, Washington, D. C., next fall) in order to understand regional implications of their continuing study. In Chicago, a Commission on Senior Citizens, whose members come from many lines of endeavor, is making headway toward better health, reduced transit fares, specially designed public housing, expanded recreational facilities, and a more enlightened retirement policy by business and industry in behalf of men and women over 65 years old. At last report, there were 70 California communities in which different citizen groups were actively engaged in programs for older persons. For ten years the University of Michigan has been gathering diverse organizations into annual conferences on aging. The university's three-day session last month, developed with the help of the Michigan State Medical Society, explored "the phenomenal increase of free time" as it affects elderly persons.

In Philadelphia, social workers, private physicians, the department of public assistance, and local hospitals have developed a system for delivering two "meals on wheels" five days a week to thousands of aged persons in a congested industrial district. One result is a reduction in the number of readmissions to Philadelphia hospitals and other institutions—readmissions once caused by the inability of many old people to obtain food or care for themselves at home. New York City has a similar program in which trained "homemakers" go to the homes of elderly people to help them in heavy cleaning.

A most ambitious cooperative effort affecting oldsters at the community level is now under way. It is the National Health Survey, launched this spring by the U. S. Public Health Service and the Bureau of the Census in selected areas of all 48 states. Comprehensive statistics on illness, as gathered by 106 doorbell-ringing interviewers, may go a long way toward solving many health problems, not simply those of today's and tomorrow's aged. Overseeing the study is a national advisory committee whose members come from organized medicine (the A. M. A.'s Dr. Mulholland included), dentistry, hospital administration, biostatics, labor, insurance agencies, pharmaceutical companies, and other interested organizations.

When Congress authorized the survey (the A. M. A. was one of many supporters) it was responding to one of the most overwhelming public issues in our local, state, and national legislative halls today. During this session of Congress alone, there have been 59 bills introduced which bear directly or indirectly on our aging population. Most of the proposed legislation dealt with creation of a federal Bureau of Older Persons, special projects to improve community services, forms of limited free hospitalization for the infirm aged, creation of study commissions, and liberalization of public assistance laws.

High Interest

Some veteran observers on Capitol Hill say that this high priority of interest in medical and other problems of the aged is "just the beginning." They predict that, on the basis of past trends, the next session of Congress in 1958 (an election year) may see the greatest volume of such legislation on record. Whatever Congress does decide, it will be responding to a large and

influential segment of the electorate; 25% are over 60 years old. New Jersey Gov. Robert B. Meynor outlined the picture concisely from a political point of view last year when he told a national conference: "We cannot afford to deal lightly with the problems of more than 13 million people over 65. No government, no political organization, can."

Our government's vital interest is best shown by the fact that after a Federal Council on Aging was created last year out of representatives from a half-dozen agencies, the President named a member of his cabinet as council chairman—Marion Folsom, Secretary of Health, Education, and Welfare. Outside of Washington, meanwhile, gerontological research is picking up both speed and scope. Where are some of the results showing up?

—At facilities of dozens of pharmaceutical houses, such as the 2 million dollar gerontological laboratory of the Wm. S. Merrell Company in Cincinnati (where yearly symposiums on aging also originate).

—At the Center for Aging Research, established within the National Institutes of Health at Bethesda, Md., to help universities and other research institutions organize a broad research program which will involve biological, sociological, and psychological mechanisms connected with aging.

—At a recently opened facility in the Menorah Home and Hospital for Aged and Infirm in Brooklyn, N. Y. It is described as the only psychiatric clinic in the nation devoted exclusively to the aged.

—At the National Institute of Neurological Diseases and Blindness in Bethesda, Md., where discussions last March underscored the hope that the aging process might eventually be susceptible to some measure of control of guidance by scientific means.

—In Birmingham, Ala., where a 20-year nutritional investigation led by Dr. Tom Douglas Spies (holder of this year's highest A. M. A. honor, the Distinguished Service Award) has returned nearly 900 feeble persons to work under the vigor of carefully planned diets particularly rich in vitamins.

How to Live Long

Strange as it may seem, scientists see research value, too, in the centenarians who have "explained" their secret of long life. Here are some of the responses: Don't argue before breakfast. Drink a pint of corn whisky with every lunch. Stay away from all liquor. You are never too old to get married. Best thing I ever did in the world was never to get married. Keep calm, read the headlines, and take walks in the summer. People would get along a lot better if they'd stop their fool worrying.

Those curious comments tend to fortify a medical conviction that sustained growth and vigor depend, to a large degree, on some positive motive for living. Without motive, a person of 35 might be "old"; with it, he might be "young" at 70 or more.

Who enjoys waiting to die? Certainly not such highly motivated individuals as 70-year-old heart specialist Paul Dudley White, 70-year-old Israel Premier David Ben-Gurion, 72-year-old former President Harry S. Truman, 73-year-old Spanish poet (last year's Nobel prize winner for literature) Juan Ramon Jimenez, 76-year-old painter Grandma Moses, Germany's 81-year-old Konrad Adenauer, 82-year-old physician-musician-

Fig. 2.—Working, playing, meditating, smiling. . . . These are scenes from a 24-minute documentary film on aging, "A Place to Live," which is being made available on free loan to medical societies and other groups through the Wm. S. Merrell Company and the National Social Welfare Assembly. (Photos from Marjory Collins-Dynamic Films, Inc.)

theologian Albert Schweitzer, 89-year-old Theodore Francis Green of Rhode Island (the oldest member ever to serve in the U. S. Senate, he still walks over three miles to and from work each day), and many other men and women whose age cannot be measured adequately by chronology. They personify the slogan of the Gerontological Society: "To add life to years, not just years to life."

Life is being added to years outside as well as inside the laboratory, the hospital research facility, and the clinical field trial site. Physicians are finding this new life, for example, in vitamin research, but—together with laymen—they are also finding it in environment studies, in more realistic retirement systems, and in functional recreation for elder citizens. While, for example, these doctors recommend the regular family environment for old folks, they recognize that this is not always possible. And so they are watching closely and hopefully the various private and public housing projects which aim to "separate but not segregate" oldsters from the beneficially bustling community life of younger people.

There has been a rash of such projects in the past few years, mounting particularly as the result of a recent federal policy which makes it easier for church denominations, labor unions, fraternal organizations, retired teacher associations, "and the like" to finance rental housing for persons over 60 years of age. Significant among these housing plans are those which reflect current medical thought on proper environment for the twilight years.

In San Francisco, for example, the Jewish Family Service Agency has an experimental housing project for older persons which provides one hot meal a day as part of the low rent. A similar project, offering the equivalent of room service at no extra cost, is operating in New York City. The Milner Hotels Management Company of Detroit announced last April that it will spend 2 million dollars to convert at least 25 of its 200 hotels into what it claims will be the nation's first hotel chain of residences for the aged. One such Milner hotel already has been operating in Fulton, Ky., with special emphasis on medical attention, entertainment, and food.

Of course, a place to live is more than brick and mortar. For the aged, it should be a roof over secure companionship—if possible, with sympathetic friends or family. To point up that need the Wm. S. Merrell Company, in cooperation with the National Social Welfare Assembly, has produced (through Dynamic Films, Inc.) a 24-minute documentary film, "A Place to Live." It is being offered on free loan to medical societies and other interested groups through either Merrell or the NSWA.

What About Retirement

Proper housing, nutrition, and recreation may be essential ingredients for aged populations in various stages of retirement, but the question of retirement itself is an overshadowing factor. What is the right retirement age? Who decides? How should it be decided? When it is decided, what form does it take—a sudden halt, or a gradual reduction in work? More importantly, should there ever be retirement from work?

The last question is of prime concern to the medical profession because no one knows better than the family physician how essential it is for elderly patients to retain the status and worth-whileness which comes with regular employment. Last spring the A. M. A. Committee on Aging decided: "It is the consensus of this committee that retirement should not be based arbitrarily on chronological age." Members unanimously took the stand that employment in all age brackets should be a matter of proper assignment of skills.

At the same time, however, the A. M. A. group is taking pioneer steps to help define when a worker's physiological capacities let down to the point where he can better serve himself and his employer by doing less rigorous work. First, the committee is trying to draft a physical examination form which might help insurance companies, industries, the armed forces, and doctors in all branches of medicine to evaluate a worker's particular capabilities. Secondly, together with other interested agencies, the committee is trying to devise an A. Q. (Aging Quotient) test based on physiological as well as psychological factors. A progress report on these two efforts is on the A. M. A. group's agenda for its meeting Sept. 15 and 16 in Washington, D. C.

"Most present-day I. Q. tests are designed for a youthful population," says Dr. Cecil Wittson, the psychiatrist member of the committee. "This does not present an accurate picture for the oldster, who may not be as speedy as younger men at a machine, but often is more reliable and has had much more experience. In addition, a battery of tests that would give a quantitative indication of the mental adaptability, judgment, and reasoning ability of aging executives could, if properly used, be of enormous value to business and to aging persons, many of whom are now forced to retire prematurely solely on the basis of their chronological age. Removal from positions of responsibility for signs of mental deterioration would also save companies from embarrassment and should be a real service to the aging employee as well as freeing him in some cases to turn to a less taxing occupation and thereby prolonging his life."

There is little doubt, from a medical standpoint, that when men have their occupations taken away many of them become lost—experiencing a distinct deterioration of personality, a marked depression, and a great acceleration in the aging process. Lack of work, even when there is a pension, almost always presents a severe problem in economics, as well, to the elderly. In Louisiana, for example, 72% of all persons over 65 are on some form of relief from local welfare depart-

ments. (The figure is only 8% in New York, largely because that state has a law holding children responsible for the support of their parents and grandparents.)

At a time when his medical needs normally are the greatest, the earning power of the oldster is at its lowest. Multiplied by the millions, it is this factor—more than any other—which challenges the entire community in every corner of our nation.

Meeting the Challenge

In many places the challenge is being met forcefully and with success. President John Erik Jonsson of Texas Instruments, Inc., has adopted a policy to "never hire anybody you don't expect to keep the rest of his working life." Some companies have established an increasing period of vacation beginning at the age of 60 with one month, and ending up at 64 with a six months vacation—so that when an employee actually retires he has had the opportunity to interest himself in another phase of life. Other firms are devising a system whereby decision for retirement is a joint responsibility of the worker's physician, the company personnel officer, the employee's job supervisor, and a disinterested fourth party. One telephone company in the Midwest puts out the "help wanted" sign for women only between the ages of 65 and 85. By specific rule, the entire faculty of the University of California's Hastings College of Law for the past decade has been made up of seasoned instructors over 65 years old (the current average age is 73.)

The New York Labor Department, in a bulletin to businesses throughout the state, recently exploded a series of myths in order to encourage the hiring of elderly workers—pointing out that as a rule they are not less productive, not more absent, not less skilled, and not necessarily too costly on the payroll, compared to younger employees. Both the National Association of Manufacturers and the United States Chamber of Commerce have shown that "the value of the productive capacity of the oldster has been grossly underestimated."

Nowhere has this concept had more precise application than in Los Angeles, where an aggressive woman of 60 not long ago discovered that senior citizens of the area owned 100 million dollars worth of local commercial investments. Since then, she has persuaded many of these security holders to protest to businesses which have discriminated against hiring older workers.

Perhaps, as one national magazine describes the movement in Los Angeles, "this may be the seed of a nationwide revolt of oldsters." If it is, then such a revolt may be long overdue. "Major tension areas have developed between the generations," says Sen. Thomas C. Desmond, chairman of the New York State Joint Legislative Committee on Problems of the Aging. "Oldsters resent being relegated to the role of baby sitters or being tolerated only as long as they serve as unpaid servants. . . . The oldster who sees no tangible evidence of direct help to him grows impatient. And why not? We tell him that help will come in time—but time is what he has the least of."

Senator Desmond's contention is that no one service, no one approach, no one type of institution will meet the needs of all elderly people at any one time or over the years. Because this denotes community effort as the key to solution of a gigantic national problem, family physicians everywhere now have the unique opportunity of creating the proper local climates of understanding in which there can be a new phase of growth and development for aging citizens. Success will come when more people are whistling while they wash their teeth.

Regression in Patient During Illness.—In every illness there is evidence of a regression to earlier phases of development, both physiologic and psychologic. That is to say, the sick person becomes more or less childlike, and is dependent, passive and demanding in his attitudes. These regressive reactions are usually reversible when one of the major factors in the particular illness has been dealt with satisfactorily. Thus, when the systemic reaction to infection or trauma begins to subside, the helplessness, clinging dependence and many other responses that have been characteristic of the particular patient's personality make-up tend to disappear. . . . Usually, physicians intuitively recognize the regression which an illness brings about, and in varying degrees they treat their patients like the children they seem to have become. The individual physician's capacity to tolerate and gratify these demands of the patient has been called his art of medicine. Doctors who do not have the capacity unconsciously to identify themselves with each of their patients must deliberately make themselves aware of their own and their patients' psychic processes. Such an awareness will make the doctor cognizant of his patient's hidden anxieties, hostilities and secondary gains. Even when the illness is severe and incapacitating, the doctor will be tactful and considerate enough to facilitate the patient's adjustment to the needed treatment, and will increase his tolerance for the ups and downs of the illness. The alleviation of the doctor's anxieties and the control of his aggressive and other tendencies will be reflected in the smoother clinical course in all illnesses and with all kinds of treatment. Thus, the traumatic effects of surgical procedures and of hospitalization can be decreased to a significant degree.—H. T. Carmichael, M.D., A Psychiatrist Looks at Problems Common to All Medical Practice, *Journal of the Iowa State Medical Society*, August, 1956.

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PRINCIPLES OF MEDICAL ETHICS—1957

In June, at its Annual Meeting in New York, the House of Delegates adopted a revision of the Principles of Medical Ethics. In contrast with previous editions of the Principles, which contained from 43 to 48 sections, the present edition consists of a preamble and 10 sections. According to the Council on Constitution and Bylaws, which drafted the new Principles, the present version "eliminates superfluous wording and matters of medical etiquette but retains all matters of ethics found in [the 1955 edition of the] Principles." These Principles are reproduced on page 1484 of this issue of THE JOURNAL.

The Judicial Council is preparing a compilation of its interpretations of the Principles of Medical Ethics issued since the turn of the century, as well as an abstract of the compilations for more general distribution. It is hoped that these documents will serve to preserve, under the 1957 Principles, the traditional ethical concepts that have been observed these many years.

The combination of a concise document stating broad, basic principles and an abstract of accepted interpretations of the Principles should eliminate the need for frequent revisions of the Principles or the necessity for adopting a code of conduct comparable to a criminal code at law.

The 1957 Principles have been thoroughly discussed at meetings of the Council on Constitution and Bylaws and before appropriate reference committees of the House. They were widely published before their adoption. They represent the combined efforts of many distinguished leaders in the field of medical ethics. Their format is a break with the immediate, verbose past and an attempt to state concisely broad guides to ethical conduct which, through interpretation, may be applied to specific factual situations.

Despite the efforts devoted to drafting this edition, and despite the full discussion of its intent and purpose, neither its length nor its language will insure observance of the principles it enunciates. At best the written principle of ethics is but the suggestion of the inexpressible. It is the effort to express truths which are known in conscience. As one's conscience is developed one knows these truths and as one follows a right conscience he acts ethically.

It is not, then, the printed document which makes a doctor ethical; rather it is his observance of the dictates of his own enlightened conscience. The document which attempts to express ethical principles is only an aid, a symbol which may help keep ideals uppermost in mind and practice. The 1957 edition of the Principles, because it is concise; because it is limited to basic, ethical concepts; and because it is capable of being displayed prominently and with pride, possesses merit as a document which can aid the doctor maintain the tradition of his profession: to do good, selflessly, as he strives to improve the health of mankind.

LENGTHENING MAN'S SPAN OF VIGOR

One by one, man through the ages has kicked over the hurdles which shorten his life: disease, malnutrition, the elements in their severity, preying beasts, and preying men. Now that humans are essentially at peace with their fellows and with nature in many areas of the globe, more people are reaching "old age" than at any time in history. But it is not always "ripe old age." Modern civilization has put up other hurdles which tend to cripple these new survivors in their longer life: tensions which hit the heart and brain, employment deprivations which hit the pocketbook, sociological problems which hit future outlook.

All of this pressure on a burgeoning population of oldsters has brought about what many authorities describe as a national problem—how to create a proper climate for senior citizens to grow with their age rather than stagnate in a tremendously expensive wait for death. Since medical science is largely responsible for this increased longevity, physicians everywhere must bear much of the burden of also prolonging man's span of activity. It is a mammoth task, calling for action and planning in many fields besides medicine. But it is a rewarding one also—for all mankind stands to benefit from the wisdom and experience of these senior citizens. They represent a relatively still-untapped source of manpower and brainpower that can be turned from an economic liability into a total asset. In the process, longevity can be extended even more fully and optimistically.

The problem in its complexity, the challenge in its urgency, and the future in its opportunity are told on page 1477 of this issue in another Medicine at Work article. Dominant in that article is the leading role physicians are playing in cooperation with lay organizations and allied health groups.

THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

Doctors and the American Medical Association frequently are berated for being "against" everything and not "for" anything. This is a hackneyed criticism that is tiresome as well as mistaken. While I generally subscribe to the philosophy that it is better to be positive than negative, I always shall oppose the wrong, the evil, and the foolish.

For example, I am against third-party intervention into medical service because it is detrimental to the doctor-patient relationship and to good medical care. From experience I know that illness is a personal problem to be solved by the patient and the doctor of his choice. In this two-party relationship there is no room for an uninterested, unsympathetic outsider. Neither the patient nor the doctor wants a third party in this personal relationship.

If my opposition to third-party intervention into medical care is labeled a defense of the medical status quo, I make no apologies. In medicine, as in anything else, there are certain basic tenets that time cannot change and that third parties should not alter or invade. One is the doctor-patient relationship, voluntarily established by the patient who chooses a physician and by the doctor who assumes responsibility for the care of the patient.

In opposing third-party intervention in medical service, we do so in favor of free choice of physician, free selection of patient, the unqualified responsibility of physician to patient, the unrestricted exercise of professional judgment, and the direct reward for individual initiative.

Through the years these freedoms have proved best for the patient, and now is the time for the medical profession to support them fearlessly for the benefit of the present and future generations.

You undoubtedly have heard critics call the principle of free choice "a vague and inconsequential" matter. I hope you take the opportunity to set them straight. Free choice is not nebulous; it is not irrelevant. Free choice is an individual liberty that enables the patient to direct the course of his own life in the pursuit of good health, long years, and personal happiness. And it is a right that helps to mold an individual's spirit of independence and self-reliance.

Doctor-patient relationship is not some obscure medical bond. It is an affirmed and legally binding mutual agreement. It is a real and personal relation in which two parties are interested primarily in one goal: the prevention or the defeat of illness and the patient's return to good health. Is there really any place for a third party interested only incidentally in this goal?

Where the doctor-patient relationship is free of outside intervention, I believe the quality of medical service is unequaled. Medicine's record of achievement in the United States as contrasted with the experiences of third-party controlled medicine in other countries proves this contention beyond any doubt.

Unhampered by third parties, the physician is free to provide the best service to his patient. He is free scientifically to apply his skills fully, without limitation or regulation; he is free personally to use his art of medicine, without interference or standardization. And his efforts are not hamstrung by extraneous rules and triplicate forms.

In this kind of relationship where both patient and physician have the maximum freedom, the matter of fees for professional service is strictly a two-party affair. Invariably, the doctor knows better than any third party what the patient should pay or what he can pay. Any standardization of fees by a third party certainly restricts the freedom of both buyer and seller of medical service. If there is to be the greatest possible physician incentive and medical competition, there can be no standardization of fees by outsiders. And if the patient is to be completely free to choose the best in the medical market, he too must not run up against restrictions arbitrarily set by third parties.

I also believe that the various freedoms of patients and physicians are tied together. Take away one or more and others inevitably are lost.

Because of recent piecemeal infringement of medicine's freedoms and patients' liberties by third parties, I am deeply concerned about the future quality of medical care. We have had the best kind of medical service in the past without third-party intervention.

For this reason I intend to resist and fight further intervention by third parties in the field of medical care and practice. In the coming year I seek your support in this effort.

DAVID B. ALLMAN, M.D., Atlantic City, N. J.

ORGANIZATION SECTION

Following are the revised Principles of Medical Ethics as adopted by the House of Delegates at the 1957 Annual Meeting.—Ed.

PRINCIPLES OF MEDICAL ETHICS

Preamble.—These principles are intended to aid physicians individually and collectively in maintaining a high level of ethical conduct. They are not laws but standards by which a physician may determine the propriety of his conduct in his relationship with patients, with colleagues, with members of allied professions, and with the public.

Section 1.—The principal objective of the medical profession is to render service to humanity with full respect for the dignity of man. Physicians should merit the confidence of patients entrusted to their care, rendering to each a full measure of service and devotion.

Section 2.—Physicians should strive continually to improve medical knowledge and skill, and should make available to their patients and colleagues the benefits of their professional attainments.

Section 3.—A physician should practice a method of healing founded on a scientific basis; and he should not voluntarily associate professionally with anyone who violates this principle.

Section 4.—The medical profession should safeguard the public and itself against physicians deficient in moral character or professional competence. Physicians should observe all laws, uphold the dignity and honor of the profession and accept its self-imposed disciplines. They should expose, without hesitation, illegal or unethical conduct of fellow members of the profession.

Section 5.—A physician may choose whom he will serve. In an emergency, however, he should render service to the best of his ability. Having undertaken the care of a patient, he may not neglect him; and unless he has been discharged he may discontinue his services only after giving adequate notice. He should not solicit patients.

Section 6.—A physician should not dispose of his services under terms or conditions which tend to interfere with or impair the free and complete exercise of his medical judgment and skill or tend to cause a deterioration of the quality of medical care.

Section 7.—In the practice of medicine a physician should limit the source of his professional income to medical services actually rendered by him, or under his supervision, to his patients. His fee should be commensurate with the services rendered and the patient's ability to pay. He should neither pay nor receive a commission for referral of patients. Drugs, remedies or appliances may be dispensed or supplied by the physician provided it is in the best interests of the patient.

Section 8.—A physician should seek consultation upon request; in doubtful or difficult cases; or whenever it appears that the quality of medical service may be enhanced thereby.

Section 9.—A physician may not reveal the confidences entrusted to him in the course of medical attendance, or the deficiencies he may observe in the character of patients, unless he is required to do so by law or unless it becomes necessary in order to protect the welfare of the individual or of the community.

Section 10.—The honored ideals of the medical profession imply that the responsibilities of the physician extend not only to the individual, but also to society where these responsibilities deserve his interest and participation in activities which have the purpose of improving both the health and the well-being of the individual and the community.

AMEF PROGRESS REPORT

In a progress report to the 19th annual meeting of the board of directors of the American Medical Education Foundation June 7 at the Waldorf-Astoria Hotel in New York City, executive secretary John W. Hedback said that foundation fund-raising from the medical profession passed the 6 million dollar mark early this year. As of May 1, 1957, contributions were up 15% over a year ago. During the rest of the year, said Hedback, his staff will help in the campaigns of those states where contributions and resources are expected to provide a major portion of AMEF income.

The A. M. A. Woman's Auxiliary's 1956-1957 campaign for the foundation was concluded at their June meeting in New York, where it was announced that $113,437.80 was raised, 26% more than the previous year. New campaign materials, four mailings to state and county Auxiliary officers, and a direct mail appeal to the entire Auxiliary membership was given major credit for the enthusiasm which produced this result.

Of marked importance among meetings arranged by the foundation in the past year was a State Chairman's Conference in Chicago, which highlighted an exchange of program procedures used in various states. It is planned to expand this sort of annual conference to include metropolitan area chairmen who can stimulate greater activity at the local level.

At a meeting of AMEF officials and alumni fund directors of several universities last March, Hedback reported, plans were made for a more cooperative effort to help medical schools. One direct result of the session was a joint campaign of Georgetown University and the foundation. A new pamphlet was designed for direct mailing to Georgetown graduates. Hope was expressed at the New York meeting that other schools would take part with AMEF in similar cooperative efforts.

Plans for the coming year include an intensive fall campaign, the showing of a newly designed AMEF exhibit at state meetings where it is requested, and a continued search for sources of large gifts to the foundation.

Elected to the board of directors at last month's annual meeting was Leland S. McKittrick of Brookline, Mass., the new Chairman of the A. M A. Council on Medical Education and Hospitals. He succeeds Herman G. Weiskotten, who is retiring. Other members of this year's AMEF Board are Louis H. Bauer, president; George F. Lull, vice-president; Edward L. Turner, secretary-treasurer; D. G. Anderson, F. J. L. Blasingame, J. W. Cline, Gunnar Gundersen, E. S. Hamilton, Victor Johnson, and J. J. Moore.

FRANK BILLINGS LECTURESHIP, AMERICAN MEDICAL ASSOCIATION

The Frank Billings Lectureship offered at annual meetings of the American Medical Association has been very popular over the years and has become well known to countless physicians throughout the country. Dr. Walter L. Bierring recently prepared a historical account of the lectureship, and it is herewith reproduced.—ED.

At the annual session of the American Medical Association in Washington, D. C., May 16-20, 1927, the Section on Practice of Medicine first considered the establishment of a special lectureship to be presented before the section each year as a part of the regular program. The matter was proposed by Dr. Henry A. Christian of Boston, and received enthusiastic support from the Chairman, Dr. Lewellys F. Barker of Baltimore and the members of the Section. The Chairman was directed to appoint five trustees to promote a special lectureship fund and institute the annual lecture as soon as possible. The following persons were named: Dr. Lewellys F. Barker, Section Chairman, 1927; Dr. Rollin T. Woodyatt, Section Chairman, 1926; and Dr. Eugene F. Kilgore, Section Chairman, 1925. These three were the present and immediate past-chairmen and constituted the Executive Committee of the Section, and therefore one trustee was changed each year. In addition, two trustees at large were named: Dr. Warfield T. Longcope and Dr. Walter L. Bierring, who served continuously. The trustees were directed to establish a special lectureship fund by voluntary subscriptions, which was quite successful, and about $4,000 was collected by September, 1929, when the financial depression made further collections rather difficult. However, small amounts were added from time to time, and in 1940 a special contribution was received from Dr. Emanual Libman of New York for $500.

At the session of the American Medical Association in 1928 in Minneapolis, the Section voted to name the annual lecture in honor of Dr. Frank Billings of Chicago in recognition of his many scientific contributions to the Section, and general eminence in American medicine.

The name of the Section on Practice of Medicine was changed in 1946 to that of Internal Medicine.

In 1941 the Frank Billings Lectureship fund was transferred to the Treasurer of the American Medical Association, 535 N. Dearborn St., Chicago. It had previously been supervised by Dr. Walter L. Bierring, as treasurer.

In order to have a trustee at large in Chicago, Dr. N. C. Gilbert was named by the Section, and upon his death in 1953 Dr. Ernest E. Irons of Chicago was selected as his successor. When Dr. Warfield T. Longcope died the same year, Dr. Walter L. Palmer of Chicago was appointed trustee at large.

The first Frank Billings Lecture was presented before the Section in 1930 at the A. M. A. session in Detroit, and has been included in the Section program at each succeeding year, with the exception of the years 1943 and 1945, when the scientific program was omitted from the annual session of the American Medical Association because of World War II.

The customary honorarium for the lecture has been $100, to which occasional additions have been made as determined by the trustees.

The following Frank Billings Lectures have been presented:

1930 Joseph L. Miller, Chicago—Detroit session.
Title—Present Status of Non-specific Therapy
THE JOURNAL, Aug. 16, 1930

1931 Henry A. Christian, Boston—Philadelphia session.
Title—Mechanism of Edema in Relation to Clinical Classification of Bright's Disease
THE JOURNAL, Aug. 1, 1931

1932 William S. Thayer, Baltimore—New Orleans session.
Title—Thoughts on Medical Education in the United States
THE JOURNAL, July 2, 1932

1933 Lewis A. Conner, New York—Milwaukee session.
Title—Development of Knowledge Concerning Role of Syphilis in Cardiovascular Disease
THE JOURNAL, Feb. 24, 1934

1934 James B. Herrick, Chicago—Cleveland session.
Title—Practitioner of Future
THE JOURNAL, Sept. 22, 1934

1935 Emanual Libman, New York—Atlantic City session.
Title—Some Aspects of Endocarditis, with Special Reference to the Subacute Variety
Not published.

1936 George Blumer, New Haven, Conn.—Kansas City session.
Title—Pericarditis Epistenocardica
THE JOURNAL, July 18, 1936

1937 Joseph A. Capps, Chicago—Atlantic City session.
Title—Air Embolism Versus Pleural Reflex as Cause of Pleural Shock
THE JOURNAL, Sept. 11, 1937

1938 Walter L. Bierring, Des Moines, Iowa—San Francisco session.
Title—Focal Infection: Quarter Century Survey
THE JOURNAL, Sept. 11, 1938

1939 George Dock, Pasadena, Calif.—St. Louis session.
Title—Historical Notes on Coronary Occlusion from Heberden to Osler
THE JOURNAL, Aug. 12, 1939

1940 E. P. Joslin, Boston—New York session.
Title—University of Diabetes: Survey of Diabetic Morbidity in Arizona
THE JOURNAL, Dec. 14, 1940

1941 Warfield T. Longcope, Baltimore–Cleveland session.
Title–Sarcoidosis or Besnier-Boeck-Schaumann Disease
THE JOURNAL, Oct. 18, 1941

1942 Joseph H. Pratt, Boston–Atlantic City session.
Title–Pancreatic Disease
THE JOURNAL, Sept. 19, 1942

1943 No scientific meeting

1944 Louis Hamman, Baltimore–Chicago session.
Title–Mediastinal Emphyzema
THE JOURNAL, May 5, 1945

1945 No scientific session

1946 Rollin T. Woodyatt, Chicago–San Francisco session.
Title–Diagnostic Problems of Diabetes

1947 E. E. Irons, Chicago–Atlantic City session.
Title–Frank Billings, Physician, Teacher, Medical Statesman, and Citizen
Bulletin of the Society of Medical History of Chicago, October, 1948

1948 James S. McLester, Birmingham, Ala.–Chicago session.
Title–Protein Comes into Its Own
THE JOURNAL, April 2, 1949

1949 Reginald Fitz, Boston–Boston session.
Title–Osler and the American Medical Association

1950 Russell M. Wilder, Rochester, Minn.–San Francisco session.
Title–Reflections on the Causation of Diabetis Mellitus
THE JOURNAL, Dec. 9, 1950

1951 N. C. Gilbert, Chicago–Atlantic City session
Title–History of Treatment of Coronary Heart Disease
THE JOURNAL, April 19, 1952

1952 George H. Coleman, Chicago–Chicago session.
Title–Present Status of Concept of Focal Infection
THE JOURNAL, Jan. 24, 1953

1953 Paul D. White, Boston–New York City session
Title–Principles and Practice of Prognosis, with Particular Reference to Heart Disease
THE JOURNAL, Sept. 12, 1953

1954 P. S. Hench, Rochester, Minn.–San Francisco session.
Title–The Cortisones and Corticotropins in General Medicine

1955 David P. Barr, New York–Atlantic City session.
Title–The Price We Pay
THE JOURNAL, Dec. 10, 1955

1956 William S. Middleton, Washington, D. C.–Chicago session.
Title–The Natural History of Disease
THE JOURNAL, Oct. 6, 1956

1957 C. Sidney Burwell, Boston–New York City session
Title–Rheumatic Heart Disease in Pregnancy

REGISTRATION AT THE ANNUAL MEETING NEW YORK, JUNE 3-7, 1957

Alabama	74	Nebraska	32
Alaska	4	Nevada	7
Arizona	38	New Hampshire	29
Arkansas	32	New Jersey	2,523
California	472	New Mexico	18
Canal Zone	5	New York City	3,614
Colorado	63	New York	4,482
Connecticut	658	North Carolina	137
Delaware	79	North Dakota	30
District of Columbia	227	Ohio	557
Florida	243	Oklahoma	44
Georgia	112	Oregon	31
Hawaii	11	Pennsylvania	1,710
Idaho	9	Puerto Rico	34
Illinois	583	Rhode Island	50
Indiana	175	South Carolina	47
Iowa	103	South Dakota	18
Kansas	45	Tennessee	103
Kentucky	85	Texas	260
Louisiana	100	Utah	23
Maine	30	Vermont	31
Maryland	337	Washington	85
Massachusetts	487	Virginia	197
Michigan	317	West Virginia	87
Minnesota	155	Wisconsin	118
Mississippi	33	Wyoming	5
Missouri	123		
Montana	11	Total	18,919

OTHER COUNTRIES

Africa	10	Iraq	2
Arabia	1	Ireland	1
Argentina	27	Israel	3
Australia	6	Italy	12
Austria	6	Jamaica	1
Bahamas	1	Japan	8
Belgium Congo	1	Korea	3
Belgium	5	Lebanon	4
Bermuda	1	Malta	1
Bolivia	2	Mexico	15
Brazil	27	Netherlands	7
Canada	142	New Zealand	2
Chile	10	Nicaragua	3
China	9	Norway	4
Colombia	7	Pakistan	2
Costa Rica	3	Peru	4
Cuba	30	Philippine Islands	16
Czechoslovakia	1	Poland	4
Denmark	6	Rhodesia	1
Dominican Republic	1	Scotland	3
Ecuador	3	Spain	8
Egypt	1	Sweden	2
El Salvador	1	Switzerland	4
England	26	Thailand	3
Finland	3	Tunisia	2
Formosa	2	Turkey	4
France	14	Uruguay	6
Germany	24	Venezuela	6
Greece	6	Virgin Islands	1
Guatemala	1	Yugoslovia	2
Haiti	2		
Honduras	2	TOTAL (other countries)	550
India	16		18,919
Indonesia	3		
Iran	10	Grand total	19,469

REGISTRATION BY SECTION

Anesthesiology	625
Dermatology & Syphilology	530
Diseases of the Chest	426
Experimental Medicine & Therapeutics	126
Gastroenterology & Proctology	308
General Practice	3,501
Internal Medicine	3,275
Laryngology, Otology & Rhinology	441
Military Medicine	162
Nervous & Mental Diseases	649
Obstetrics & Gynecology	1,022
Ophthalmology	823
Orthopedic Surgery	518
Pathology & Physiology	435
Pediatrics	855
Physical Medicine & Rehabilitation	177
Preventive & Industrial Medicine & Public Health	344
Radiology	602
Surgery, General & Abdominal	2,080
Urology	366
Session on Allergy	150
Session on Legal Medicine	21
Session on Medical Communication	14
More than one section	176
No section checked	1,853
Total	19,469

MEDICAL NEWS

CALIFORNIA

Dr. Newell Honored.—Radiologists and other colleagues gathered in San Francisco on June 17 at a testimonial dinner honoring Dr. Robert Reid Newell on his retirement as professor of medicine and biophysics, Stanford University School of Medicine. A Festschrift issue of the *Stanford Medical Bulletin*, containing contributed papers of general interest in the fields of radiology, radiobiology, and biophysics, is being prepared in his honor for release in August. Dr. Newell has served on the International Committee on Radiation Protection, Committee on Radiologic Units, Standards and Protection of the American College of Radiology. He is a past-president (1951) and fellow of the American College of Radiology.

Brain-Oxygen Research Grant.—The College of Medical Evangelists, Los Angeles, has received an $18,499 grant from the National Institutes of Health. According to Dr. Findlay E. Russel, director of the college's Laboratory of Neurological Research at Los Angeles County Hospital, the grant is for a study "designed to determine the changes produced in discrimination by the various senses, shifts in emotional response to certain stimuli, and variations in patterns of timing when the brain is subjected to an oxygen lack." The team of investigators, including Dr. Cyril B. Courville, Dr. Ralph Gunter, and Dr. Russell, will also observe differences in behavior produced by poisoning from various gases which cause a deficiency of oxygen in the brain.

Cardiovascular Research Institute.—Construction will begin this month on quarters for the new Cardiovascular Research Institute at the University of California Medical Center, San Francisco. The institute will occupy the presently unfinished 13th floor of the Herbert C. Moffitt Hospital. The institute's laboratories and research beds will provide the environment for an extensive program of basic and applied research on diseases involving the heart and circulatory system. Members of many School of Medicine departments will cooperate in investigating a broad range of cardiovascular problems. The floor will be completed at a cost of about $460,000 provided by the California Legislature and the United States Department of Health, Education, and Welfare. Construction is scheduled to be completed by April 30, 1958.

GEORGIA

Appoint Chairman of Department of Medicine.—Dr. Thomas Findley, who has been professor of medicine and chairman of cardiovascular research for the Georgia Heart Association at the University of Georgia School of Medicine, Augusta, since May, 1954, has been named chairman of the department of medicine, effective July 1, when Dr. Virgil P. Sydenstricker retired. Dr. Sydenstricker has been professor of medicine and chairman of the department since 1922. Dr. Findley was made head of the section of Internal Medicine at the Ochsner Clinic in New Orleans in 1942. He also served on the faculty of Tulane University School of Medicine, being appointed professor of clinical medicine, which position he held until coming to the Medical College of Georgia. Dr. Findley was secretary-treasurer and subsequently president of the Southern Society for Clinical Research; president of the New Orleans Academy of Internal Medicine in 1947; and in 1950 was a member of the Board of Governors of the American College of Physicians. Since 1952, he has been secretary-treasurer of the American Board of Internal Medicine.

ILLINOIS

Chicago

Society News.—At a recent meeting of the German Medical Society of Chicago the following officers were elected for the year 1957-1958: president, Dr. Ferdinand Seidler; vice-president, Dr. Joseph R. Mueller; secretary, Dr. Eugene F. Lutterbeck; and treasurer, Dr. Edward V. Stalzer.

Dr. Vail Honored.—Dr. Derrick T. Vail, chairman, department of ophthalmology, Northwestern University Medical School, has been honored at Oxford, England, for his contributions in ophthalmology. The Oxford Ophthalmological Congress was founded in 1909 by Robert Doyne, a British ophthalmologist. Each year an international council invites an eye surgeon to deliver the Doyne Memorial Lecture and to receive the Doyne Medal. Dr. Vail is the second American in the history of the congress to be so honored. Subject of his address to the group was the zonule membrane. Dr. Vail has received the Legion of Merit, the Bronze Star Medal, the Order of the Crown of Belgium, and the Medal of Gratitude from France. He is an honorary member of the Ophthalmological Society of the United Kingdom and honorary fellow of the Royal College of Surgeons.

MAINE

Society News.—At the recent meeting of the Maine Radiological Society the following officers were elected: president, Dr. John T. Konecki, Lewiston; vice-president, Dr. Irving L. Selvage, Portland; and secretary-treasurer, Dr. Francis J. O'Connor, Augusta.

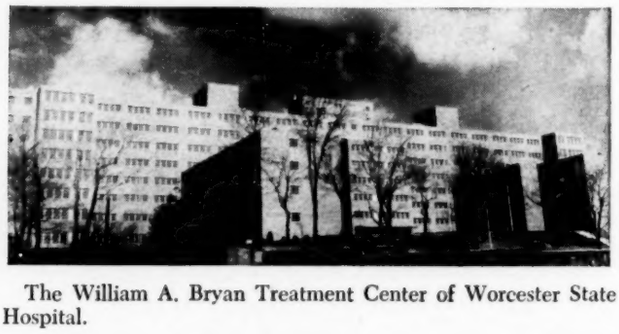
Cancer Research Fellowships.—The Maine Cancer Society has recently awarded 12 special fellowships for an intensive course at the New York Memorial Center for Cancer Research to Maine physicians and administrators of hospitals who are also registered nurses. The physicians were Dr. Armand Albert, of Van Buren, president of the Maine Medical Association; Dr. Richard C. Wadsworth, of Bangor, pathol-

ogist at Eastern Maine General Hospital, and Dr. John F. Reynolds, of Thayer Hospital, Waterville, both of whom are members of the Maine Cancer Society board of directors; and Dr. Charles D. McEvoy Jr., of Eastern Maine General Hospital, Boothbay Harbor.

MASSACHUSETTS

Personal.—Albert Baird Hastings, Ph.D., Hamilton Kuhn Professor of Biological Chemistry, Harvard Medical School, Boston, has been named visiting professor of biochemistry at the Australian National University, Canberra. Professor Hastings began lecturing and conducting seminars at the Australian university for a three-month period starting July 1. He will also lecture in Melbourne and Sidney.

Open Worcester Treatment Center.—Recently the William A. Bryan Treatment Center of Worcester State Hospital opened for the treatment of psychiatric cases. It has a capacity of 860 patients and includes a day hospital, night hospital, and outpatient department. Built at a cost of 7 million dollars, the seven-story center features a large auditorium, a 400-bed psychiatric area, complete operating room, obstetrical



The William A. Bryan Treatment Center of Worcester State Hospital.

service, nursery, dental suites, x-ray and physiotherapy facilities, and interview rooms. The upper four stories are devoted to medical and surgical service. Of the 32 psychiatric wards, 22 are open to allow patients to go outdoors or go to the patients' recreation center. Superintendent of the hospital is Dr. Bardwell H. Flower.

Professorship in Gynecology.—The Joe Vincent Meigs Fund for the establishment of a professorship in gynecology at the Harvard Medical School, Boston, has been announced. The professorship is named in honor of Dr. Joe Vincent Meigs, professor of gynecology in the Harvard Faculty of Medicine, who retired as chief of staff of the Vincent Memorial Hospital and chief of gynecologic service of the Massachusetts General Hospital to become visiting gynecologist to both institutions. A report from the Harvard Medical School states that the Vincent laboratory was started by Dr. Meigs and Dr. Maurice Fremont-Smith in the early 1940's. In supporting collaborative research, the Joe Vincent Meigs Fund for teaching and research in gynecology was conceived. For information write: The Joe Vincent Meigs Fund, 24 Milk St., Boston, Mass.

MINNESOTA

Personal.—Dr. Joyce S. Lewis has been named director of the Hamm Memorial Psychiatric Clinic, St. Paul. Dr. Lewis succeeds Dr. Clarence J. Rowe, who resigned to enter private practice. Dr. Rowe has also accepted an assignment as a psychiatric consultant at the clinic, thus filling a post which has been open for some time. Dr. Lewis, who has served as instructor of psychiatry will continue as a clinical instructor in the department of psychiatry, University of Minnesota Medical School, Minneapolis.

Cancer Research Training Programs.—Two training programs in cancer research at the University of Minnesota Medical School, Minneapolis, have been announced. The programs are sponsored by the National Cancer Institute of the Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, and are administered by the departments of physiological chemistry, physiology, and pathology and by the department of bacteriology and immunology. The programs are designed to provide training in experimental cancer research for predoctoral and postdoctoral candidates in the basic disciplines of pathology, physiology, physiological chemistry, microbiology, immunology, and cell culture. A coodinated teaching and research program has been organized within the four departments. Information may be obtained from Mr. John F. Van Pilsum, Program Training Director, Department of Bacteriology and Immunology, University of Minnesota Medical School, Minneapolis.

NEW YORK

Society News.—At the annual meeting of the New York Academy of Gastroenterology the following officers were elected for 1957-1958: president, Dr. Jerome A. Marks; president-elect, Dr. Milton J. Matzner; first vice-president, Dr. Michael Weingarten; second vice-president, Dr. Joseph R. Van Dyne; secretary, Dr. Alexander Slanger; recording-secretary, Dr. Jerome Weiss; and treasurer, Dr. William C. Jacobson.

NORTH CAROLINA

State Medical Election.—The following officers of the North Carolina Medical Society have been elected: president, Dr. Edward W. Schoenheit, Asheville, succeeding Dr. Donald B. Koonce, Wilmington; president-elect, Dr. Lenox D. Baker; and vice-presidents, Dr. Amos N. Johnson, Garland, and Dr. George Holmes, Winston-Salem.

OHIO

Muscular Dystrophy Clinic.—Establishment of a new Muscular Dystrophy Clinic in Cincinnati, with a $10,000 allocation from Muscular Dystrophy Associations of America, Inc., has been announced. The new clinical facility, installed at the Children's Convalescent Hospital and Rehabilitation Center, University of Cincinnati College of Medicine, is under the direction of Dr. John E. Allen. The clinic will begin serving an estimated 50 child patients, with additional children and adults with muscular dystrophy and allied diseases

to be drawn from neighboring Kentucky and Indiana. The grant is part of the latest dystrophy associations allocations, totaling $165,512 to support research and to establish or maintain clinic services.

PENNSYLVANIA

Society News.—The following officers were elected at the annual session of the Pittsburgh Roentgen Society: president, Dr. Erwin Beck; vice-president, Dr. Harrison Richardson; secretary, Dr. Edward M. Schultz; and treasurer, Dr. James Hayes.

Philadelphia

Personal.—Marion Spencer Fay, Ph.D., dean of the Woman's Medical College of Pennsylvania, received an honorary degree of doctor of medical science from Beaver College at their 104th commencement exercises. Dr. Fay, coming to the Woman's Medical College in 1935, has served as dean of this institution since 1943.

SOUTH CAROLINA

Society News.—The members of the South Carolina Radiological Society have elected the following officers: president, Dr. William Klauber; vice-president, Dr. Samuel Fisher; and secretary-treasurer, Dr. Wayne Reeser.

WASHINGTON

State Association Meets in Seattle.—The 68th annual convention of the Washington State Medical Association will be held in the Olympic Hotel, Seattle, Sept. 15-18. Dr. Gunnar Gundersen, of La Crosse, Wis., president-elect of the American Medical Association, will be a speaker. Four half-day symposiums will be conducted on Sept. 17 and 18 on the subjects of noise in industry, office management of joint disease, prenatal problems, and trauma of the hand. The following papers will be presented by out-of-state guest speakers:

The Doctor and the Industrial Noise Problem, Dr. Aram Glorig Jr., Los Angeles.

The Management of Three Common Joint Diseases—Rheumatoid Arthritis, Osteoarthritis and Gout, Dr. Charles Ragan, New York.

Recent Laboratory Tests for Rheumatoid Arthritis, Dr. John P. Wallace Thomas, Vancouver, B. C.

The Early Recognition of Difficult Labor, Dr. D. Frank O. Kaltreider, Baltimore.

Bleeding in the First Trimester, Dr. Ralph C. Benson, Portland, Ore.

Early Care of Open Hand Injuries, Dr. Michael L. Mason, Chicago.

An annual golf tournament and salmon fishing derby are planned. For information write Dr. James H. Berge, president, Washington State Medical Association, 1309 Seventh Ave., Seattle 1, Wash.

WISCONSIN

Viral and Rickettsial Symposium.—The University of Wisconsin School of Medicine has announced a symposium on latency and masking in viral and rickettsial infections to be held on the campus Sept. 4-6. The purpose of the symposium is to consider recent information in human, animal, and plant systems that bear on the interaction between host cell, infecting agent, and the cellular environment. The program is divided into three general discussion areas after a keynote address by Dr. Christopher H. Andrewes, of London, England. The first day will be devoted to "Viral Characteristics Leading to Masking and Latency," the second to "Factors of Host Cell and Environment to Masking and Latency," and the third to "The Role of Inhibitors in Masking and Latency." A final summary and critique is scheduled for the final afternoon to discuss common terminology and the present concepts of mechanism. Participants include Dr. Andrewes and F. C. Bawden, from England, A. Lwoff, from France, and C. H. Berghold, from Canada. For information write Dr. A. S. Evans, Division of Preventive Medicine, University of Wisconsin Medical School, Madison, Wis.

WYOMING

State Medical Election.—At the annual meeting of the Wyoming State Medical Society the following officers were elected: president, Dr. Harlan B. Anderson, of Casper; president-elect, Dr. Luther H. Wilmoth, of Lander; vice-president, Dr. Benjamin Gitlitz; secretary, Dr. Francis A. Barrett, Cheyenne; and treasurer, Dr. Carleton D. Anton, of Sheridan.

GENERAL

Medical Research Fellowships and Grants.—Applications for awards available July 1, 1958, will be received by the Life Insurance Medical Research Fund as follows: (1) Until Oct. 15, for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend is $3,800, with allowances for dependents and necessary travel. (2) Until Nov. 1, for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. About $1,000,000 will be available for the two types of award. Information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 E. 46th St., New York 17.

Pediatric Cardiology Fellowship.—A clinical fellowship in pediatric cardiology is offered in the department of pediatrics of the Yale University School of Medicine, New Haven, Conn. The stipend is $4,500 per annum but the candidate must be a United States citizen and have had at least two years of pediatric training. Pediatric cardiac diagnostic and follow-up clinics, consultations, and assistance in the care of cardiac surgical patients will be offered, together with the performance of various diagnostic examinations and assistance with research in the cardiovascular laboratory. The applicant should correspond with Dr. Milton J. E. Senn, professor of pediatrics, or Dr. Ruth Whittmore, Director, New Haven Rheumatic Fever and Cardiac Program, Department of Pediatrics, Grace–New Haven Community Hospital, 333 Cedar St., New Haven 11, Conn.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	June 29, 1957 Paralytic Type	June 29, 1957 Total Cases	June 30, 1956 Total Cases
New England States			
Maine	...	...	...
New Hampshire	...	...	...
Vermont	...	...	...
Massachusetts	...	...	...
Rhode Island	...	...	...
Connecticut	...	2	...
Middle Atlantic States			
New York	3	6	13
New Jersey	...	3	6
Pennsylvania	...	1	1
East North Central States			
Ohio	...	...	2
Indiana	2	2	2
Illinois	...	2	21
Michigan	1	3	10
Wisconsin	...	1	5
West North Central States			
Minnesota	...	...	2
Iowa	...	2	1
Missouri	...	1	8
North Dakota	...	...	1
South Dakota	...	1	1
Nebraska	...	...	2
Kansas	...	...	4
South Atlantic States			
Delaware	...	...	...
Maryland	...	...	2
District of Columbia	...	...	1
Virginia	...	...	6
West Virginia	1	1	...
North Carolina	...	1	1
South Carolina	2	7	2
Georgia	2	3	3
Florida	2	5	17
East South Central States			
Kentucky	...	...	...
Tennessee	3	16	2
Alabama	...	3	2
Mississippi	...	3	7
West South Central States			
Arkansas	1	4	2
Louisiana	5	12	20
Oklahoma	...	6	7
Texas	19	39	41
Mountain States			
Montana	...	...	3
Idaho	...	...	1
Wyoming	...	2	2
Colorado	...	...	5
New Mexico	...	...	1
Arizona	...	1	...
Utah	...	1	2
Nevada	...	...	...
Pacific States			
Washington	...	...	1
Oregon	...	...	...
California	1	14	50
Territories and Possessions			
Alaska	...	...	...
Hawaii	...	...	...
Puerto Rico	...	...	3
Total	42	142	260

Medico-Legal Seminar.—The annual Belli Seminar was held in New York City, July 5-6. The seminar included discussions of the law for the trial lawyer trying all phases of legal cases from taxation to and including personal injury law. The informal seminar featured cases and experiences presented by physicians as well as lawyers, and slides, among other things, surgical operations and fact investigations. Specialists in pathology, toxology, psychiatry, obstetrics, pediatrics, surgery, and other fields discussed their particular functions. Among the speakers were Dr. Paul D. Kantor, professor of law, Georgetown University, and a general practitioner, and Dr. Nicholson Eastman, head, obstetrics, Johns Hopkins Hospital, who spoke on "Trauma in Obstetrics." Information may be obtained from Melvin M. Belli, TWA Building, 240 Stockton Street, San Francisco 8, Calif.

Multiphasic Screening Tests.—A recent release from the Public Health Committee of the Medical Society of the County of Kings reported that 63 members of the society were given screening tests during the evening of Dec. 18, 1956, while a meeting was in progress. A chest x-ray, urinalysis, blood smear, height and weight, blood pressure reading, and electrocardiogram were taken. Each doctor received a number which made the examinations and results confidential. A team of experts in their respective fields analyzed each laboratory procedure, whereas the complete examination was analyzed and reported back by a team of internists. Of a total of 59 completed examinations, made up of this random sample, 10 had no knowledge of definite heart disease. Eight others had suspicious findings to justify further study. Seven had lung disease of remote origin and two of recent origin that was not revealed by the doctor in his screening history. Nine had hypertension without previous knowledge of this disturbance. Three urinalyses were positive for albumin and one for sugar. These findings were reported back to the doctor for further investigation. Twenty-four (40%) of those examined were found to be obese.

Personal.—Announcement has been made of the appointment of Thomas Harrison Davies, Ph.D., as a director of research of the Mellon Institute, Pittsburgh. Dr. Davies has been the administrative head of the Multiple Fellowship sustained in the institute since 1952 by the Pittsburgh Plate Glass Company. Prior to joining Mellon Institute Dr. Davies was an associate professor in the Institute for Nuclear Studies, in the Department of Chemistry, and in the Institute of Radiobiology and Biophysics of the University of Chicago.——The National Academy of Sciences has announced that Dr. George Darling, professor of human ecology, Yale University, New Haven, Conn., has been named director of the Atomic Bomb Casualty Commission, with headquarters in Hiroshima and Nagasaki, Japan. The commission, which is operated by the National Academy of Sciences in close cooperation with the Japanese government, has since 1946 been conducting long-term studies of Hiroshima and Nagasaki populations to identify any latent biological effects from the ionizing radiation of the atomic bomb of World War II. Professor Darling has served as executive secretary of the Academy and Research Council. In 1946, he became director of medical affairs at Yale, a post which he retained until his appointment to the newly established professorship of human ecology in 1952. In his new position Professor Darling will be succeeding Dr. Robert H. Holmes, retiring after three years as director.

Society News.—The following officers of the **American Diabetes Association** were elected for the organizational year 1957-1958: president, Dr. John A. Reed, Washington, D. C.; first vice-president, Dr. Alexander Marble, Boston; second vice-president, Dr. Francis D. W. Lukens, Philadelphia; secretary, Dr. Franklin B. Peck Sr., Indianapolis; and treasurer, Dr. William H. Olmsted, St. Louis.——At a recent meeting of the **American Radium Society** the following officers were elected for the year 1957-1958: president, Dr. Ralph T. Ogden, Hartford, Conn.; president-elect, Dr. Milford D. Schulz, Boston; first vice-president, Dr. Ralph M. Caulk, Washington, D. C.; second vice-president, Elizabeth F. Focht, New York City; secretary, Dr. Theodore R. Miller, 139 East 36th St., New York 16; and treasurer, Dr. Jesshill Love, Louisville. The 40th annual meeting of the society will be held March 27-29, 1958, at the Hollywood Beach Hotel, Hollywood Beach, Fla.——At the annual meeting of the **American Goiter Association** held recently the following officers were elected: president, Dr. Elmer C. Bartels, Boston; president-elect, Dr. Warren H. Cole, Chicago; first vice-president, Dr. William P. Kroger, Los Angeles; second vice-president, William L. Money, Ph.D., New York City; third vice-president, Dr. Mavis P. Kelsey, Houston, Texas; secretary, Dr. John C. McClintock, Albany, N. Y.; and treasurer, Edwin G. Ramsdell, White Plains, N. Y. The next annual meeting of the association will be held in San Francisco June 17-19, 1958.——At the second annual meeting of the **Flying Physicians Association** the following officers were elected: Dr. Samuel D. Sullennerger, Dandridge, Tenn., president; and Drs. Charles M. Starr, North Hollywood, Calif.; Donald W. Smith, Miami, Fla.; Gordon Jones, Olympia, Wash.; Charles H. Loomis, Richmond, Ind.; John J. Quinlan, Brantford, Ont.; James Y. Bradfield, Dallas, Texas, vice-presidents.——Recently the following officers of the **Association of Surgeons of the Southern Railway System** were elected: president, Dr. Cecil E. Newell, Chattanooga, Tenn.; first vice-president, Dr. Battle Malone II, Memphis, Tenn.; second vice-president, Dr. Sam Orr Black, Spartanburg, S. C.; third vice-president, Dr. Arthur B. Bradsher, Durham, N. C.; fourth vice-president, Dr. Walter R. Brewster, New Orleans; recording secretary, Dr. John M. Frere Sr., Chattanooga; and secretary-treasurer, Dr. William J. Ashton, Washington, D. C.——Officers of the **American Surgical Association** for the coming year are as follows: president, Dr. John H. Mulholland; first vice-president, Dr. Richard K. Gilchrist; second vice-president, Dr. Henry N. Harkins; secretary, Dr. William A. Altemeier; treasurer, Dr. John C. Burch; and recorder, Dr. John E. Dunphy.——At the 18th annual meeting of the **Society for Investigative Dermatology** the following officers were elected: president, Dr. Walter C. Lobitz Jr., Hanover, N. H.; vice-president, Dr. Hermann K. B. Pinkus, Monroe, Mich.; and secretary-treasurer, Dr. Herman Beerman, Philadelphia.

CORRECTION

Use of Artificial Kidney After Poisoning.—In the letter to the Editor on the use of artificial kidney, in THE JOURNAL, June 22, page 916, in the 10th line of the first paragraph, "25 mg." should have read "25 Gm."

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Part I.* Various Centers, Sept. 3-4. Sec., Dr. John B. Hubbard, 133 South 36th St., Philadelphia 4.

MEDICAL SPECIALTY BOARDS

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral.* Washington, Oct. 28-Nov. 1. Sec., Dr. Curtiss B. Hickcox, 80 Seymour St., Hartford 15.

AMERICAN BOARD OF DERMATOLOGY: *Oral.* Baltimore, Oct. 11-13. Final date for filing application was April 1. Sec., Dr. Beatrice Maher Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 21. *Oral.* Los Angeles, Sept. 11-14. Final date for filing applications was Feb. 1. Exec. Sec., Dr. W. A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Part I.* Chicago, Jan. 2. *Part II.* Chicago, May 7-17. Final date for filing application is September 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* Chicago, Oct. 7-11. *Written.* January 1958. Final date for filing application was July 1. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part II.* New York City, Jan. 29-31, 1958. Final date for filing application is August 15. Sec., Dr. Sam W. Banks, 116 South Michigan Avenue, Chicago 3.

AMERICAN BOARD OF OTOLARNGOLOGY: Chicago, Oct. 7-11. Final date for filing application was in April. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Oral and Written. Pathologic Anatomy and Clinical Pathology.* New Orleans, Sept. 26-28. Final date for filing application is August 15. Sec., Dr. Edward B. Smith, Indiana University Medical Center, Indianapolis 7.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written Examination.* San Francisco, Oct. 31-Nov. 2. Final date for filing case reports was July 1. Corresponding Sec., Miss Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written. Parts I and II.* September. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York, Dec. 16-17. San Francisco, March 17-18. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S. W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Washington, Sept. 23-28. Final date for filing application was June 1. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part II.* Buffalo, Sept. 23-24; New Haven, Oct. 21-23; Indianapolis, Nov. 18-19; Cincinnati, Dec. 16-17; New Orleans, Jan. 13-14; Durham, N. Car., Feb. 10-11; Baltimore, March 10-11; Chicago, May 12-13; Los Angeles, June 16-17 and Portland, Oregon, June 20-21. Sec., Dr. John B. Flick, 225 So. 15th St., Philadelphia 2.

AMERICAN BOARD OF UROLOGY: *Written examination.* Various cities throughout the country. *Pathology and Oral Clinical.* February 1958. Location not decided. Exec. Secretary, Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 16.

BOARD OF THORACIC SURGERY: *Written.* Various centers throughout the country, September 1957, and the closing date for registration was July 1, 1957. Sec., Dr. William H. Tuttle, 1151 Taylor Ave., Detroit 2.

DEATHS

Van Kleeck, Louis Ashley, Great Neck, N. Y.; born in 1887; Cornell University Medical College, New York City, 1909; an associate member of the American Medical Association and in 1935, 1940, 1944, and 1947 a member of its House of Delegates; past-president and vice-president of the New York State Association of School Physicians; past-president of the Nassau County Medical Society and the Second District Branch of the Medical Society of the State of New York; fellow of the American College of Physicians, American Academy of Pediatrics, and the Brooklyn Academy of Pediatrics; for many years associated with the Nassau Hospital in Mineola, Meadowbrook Hospital in Hempstead, and St. Francis Hospital and Sanatorium for Cardiac Children in Roslyn; formerly school physician in the Manhasset public schools; a founder, a director, and vice-president and president of the First National Bank and Trust Company of Manhasset, now the Manhasset branch of the Meadow Brook National Bank; died in New York Hospital April 30, aged 69, of hypertensive cardiovascular disease.

Yudkin, Arthur Meyer ✱ New Haven, Conn.; born in Ansonia in 1892; Yale University School of Medicine, New Haven, 1917; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology, American Ophthalmological Society, and the Association for Research in Ophthalmology; clinical professor of ophthalmology at his alma mater; past-president of the Association of Yale Alumni; associated with Grace–New Haven Community Hospital and the Hospital of St. Raphael; an associate editor of "Practitioners' Library of Medicine and Surgery"; died in Wallingford May 2, aged 65, of a heart attack.

Chase, William Wiley ✱ Washington, D. C.; born in Baltimore June 5, 1901; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1927; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; veteran of World War II; in 1955 awarded an honorary doctor of science degree by Western Maryland College, Westminster, of which he was a board member; associated with the George Washington University Hospital and the Garfield Memorial Hospital, where he died May 16, aged 55, of bronchogenic carcinoma.

Hardison, Thomas William ✱ Morrilton, Ark.; born in 1884; (licensed in Arkansas, 1905); past-president of the Conway County Medical Society; served as a member and chairman of the State Park Commission; a member of the Arkansas Resources and Development Commission and chairman of its park committee from 1945 to 1953; held an honorary doctor of laws from Hendrix College; received the Cornelius Amory Pugsley Medal from the American Scenic and Historic Preservation Society; served as county health officer; on the honorary staff, St. Anthony's Hospital, where he died April 7, aged 73, of infectious hepatitis.

✱ Indicates Member of the American Medical Association.

Hopkins, Brewster Arthur ✱ Stuart, Va.; born in Buffalo Ridge, Dec. 5, 1903; Medical College of Virginia, Richmond, 1929; interned at the City Memorial Hospital in Winston-Salem, N. C., and later senior assistant physician at the Central State Hospital in Petersburg; past-president of the Patrick–Henry Counties Medical Society; member of the American Academy of General Practice; one of the organizers and for many years member of the board of directors of the Virginia Academy of General Practice; on the staff of the Stuart Hospital; died April 22, aged 53, of coronary thrombosis.

Peggs, Harry MacDonald ✱ St. Albans, Vt.; born in Swanton in 1878; Baltimore University School of Medicine, 1900; fellow of the International College of Surgeons; formerly practiced in Staten Island, N. Y., where he was co-founder and chief surgeon at the Richmond Memorial Hospital and on the staff of St. Vincent's Hospital; associated with the Fanny Allen Hospital in Winooski, and St. Albans and Kerbs Memorial hospitals; for many years a director of the Tottenville National Bank in Staten Island, died in the Mary Fletcher Hospital, Burlington, April 20, aged 78, of pneumonia.

Richards, Samuel Burgess ✱ San Bernardino, Calif.; born in Carrsville, Ky., Feb. 3, 1881; College of Physicians and Surgeons, Los Angeles, 1906; fellow of the American College of Surgeons; past-president of the San Bernardino County Medical Society; served as county health officer; at one time practiced in Victorville, where he was a member of the school board; formerly medical superintendent of the San Bernardino General Hospital; associated with St. Bernardine's and San Bernardino County Charity hospitals; died May 5, aged 76, of myocardial infarct and coronary arteriosclerosis.

Smith, Herbert Leander, Watertown, N. Y.; born in Rutland, N. Y., Aug. 26, 1863; University of Buffalo School of Medicine, 1888; an associate member of the American Medical Association; served as county coroner, county physician, and as health officer of Watertown; associated with the House of the Good Samaritan and Mercy Hospital; for many years medical superintendent of the Jefferson County Tuberculosis Sanatorium, now known as the Jefferson County Sanatorium and Hospital for Chronic Diseases, where he was on the staff, and where he died March 19, aged 93, of uremia and arteriosclerosis.

Tabor, Gilbert Stevens ✱ Millerton, N. Y.; born in Dover Plains, Aug. 17, 1898; University and Bellevue Hospital Medical College, New York City, 1919; past-president of the Dutchess County Medical Society; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology and the American Oto-rhinologic Society for Plastic Surgery; village health officer; on the staff of the Sharon (Conn.) Hospital; a director of the Millerton National Bank; died April 4, aged 58, of liver abscesses secondary to carcinoma of the duodenum.

Hyatt, Robert Fee Jr. ✦ Monticello, Ark.; University of Arkansas School of Medicine, Little Rock, 1939; member of the American Academy of General Practice; member of the school board; veteran of World War II; member and past-president of the Rotary Club; served as director of the Chamber of Commerce; received the Silver Beaver Award for his service in the Boy Scouts; died April 11, aged 45, when the automobile in which he was riding plunged off an embankment near Hampton into backwaters of the swollen Quachita River.

McElroy, Joseph Dean ✦ Atlanta, Ga.; born in Atlanta Sept. 6, 1915; Medical College of Georgia, Augusta, 1941; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; recently appointed a member of the advisory committee for the mental hygiene division of the Georgia Health Department; served on the faculty of Emory University School of Medicine; veteran of World War II; associated with Grady Memorial and Crawford W. Long hospitals and St. Joseph's Infirmary; died April 26, aged 41.

Pate, James Gibson ✦ Gibson, N. C.; University of Pennsylvania School of Medicine, Philadelphia, 1916; past-president of the Scotland County Medical Society; for many years member of the Scotland County Welfare Board and a member of the school board of Gibson; chairman of the board of the Commercial State Bank; past-president of the Bank of Gibson; served on the staffs of the Marlboro County Hospital in Bennettsville, S. C., and the Scotland County Memorial Hospital, Laurinburg, where he died April 19, aged 65, of carcinoma of the prostate.

Sabine, Ralph Stoddard ✦ Murphysboro, Ill.; St. Louis University School of Medicine, 1908; member of the American Academy of General Practice; an associate member of the International College of Surgeons; past-president of the Southern Illinois Medical Association; veteran of World War I; past-president of the Murphysboro Chamber of Commerce and the Murphysboro Rotary Club; surgeon for the Missouri Pacific Railroad Company; on the staff of St. Andrew's Hospital, where he died April 6, aged 75, of coronary occlusion.

Turner, William Preston Sr. ✦ Greenwood, S. C.; born in Cross Hill, April 6, 1881; University of Georgia Medical Department, Augusta, 1904; fellow of the American College of Surgeons; for many years commissioner of public works; served on the board of the Connie Maxwell Children's Home; on the staff of the Self Memorial Hospital; past-president of the Greenwood Rotary Club and in 1953 received its "Man of the Year" community service award as "an outstanding practitioner of the Rotary creed 'service above self' "; died April 2, aged 75, of cerebral hemorrhage.

Casebeer, Harvey Lee ✦ Butte, Mont.; University of Nebraska College of Medicine, Omaha, 1933; member of the Industrial Medical Association; past vice-president of the Montana Medical Association; past-president of the Silver Bow County Medical Society and the Montana Academy of Oto-Ophthalmology; associated with St. James Hospital; a director and past-president of the Butte Chamber of Commerce; died April 27, aged 49, of injuries received in an automobile accident.

Clovis, Elijah Ellsworth ✦ Wheeling, W. Va.; College of Physicians and Surgeons, Baltimore, 1905; member of the American Trudeau Society; fellow of the American College of Physicians; from 1912 to 1924 superintendent of the Hopemont (W. Va.) Sanitarium, of which he was a founder; for many years superintendent of the Ohio County Sanitarium; served as medical director of the Conservative Life Insurance Company; died May 13, aged 77, of arteriosclerotic heart disease.

Hayt, Ralph Augustus, Fishkill, N. Y.; born Nov. 11, 1877; Columbia University College of Physicians and Surgeons, New York City, 1900; veteran of the Spanish–American War; served as consulting surgeon at the Matteawan State Hospital in Beacon; at one time on the staff of the Veterans Administration Hospital in Castle Point; formerly on the courtesy staffs of Vassar Brothers and St. Francis hospitals in Poughkeepsie; until his retirement associated with Highland Hospital in Beacon, where he died April 5, aged 79.

Loeb, Ludwig, Philadelphia; Jefferson Medical College of Philadelphia, 1890; an associate member of the American Medical Association; co-founder and for many years medical director of the National Stomach Hospital; co-founder of the American Hospital for Diseases of the Stomach; for many years associated with the Jewish Maternity and Jewish hospitals; served as consulting physician at the Mount Sinai Hospital; died in the Pennsylvania Hospital May 4, aged 91.

O'Brien, Augustus Joseph ✦ Ironwood, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1908; also a graduate in pharmacy; fellow of the American College of Surgeons; past-president of the American Association of Railway Surgeons; served as surgeon for the Soo Line and Chicago and Northwestern railroads; on the staff of Grandview Hospital; for many years a director of the Gogebic National Bank; died in Divine Infant Hospital, Wakefield, April 23, aged 74, of coronary occlusion.

Oppenheimer, Seymour, New York City; University of the City of New York Medical Department, New York City, 1892; specialist certified by the American Board of Otolaryngology; member of the New York Academy of Medicine; served on the staffs of the Monmouth Memorial Hospital in Long Branch, N. J., and the Gouverneur, Sydenham, Bellevue, Willard Parker, and Mount Sinai hospitals, and the Hospital for Joint Diseases; died in St. Luke's Hospital April 21, aged 84, of carcinoma of the kidney.

Tressel, Henry Arthur ✦ Wakefield, Mich.; Northwestern University Medical School, Chicago, 1911; for many years served on the board of education; Wakefield township school physician; for many years city health officer; until 1956 chief of staff at the Divine Infant of Prague Hospital, where he was an active staff member; the city of Wakefield named a park in his honor; died in the Fairview Hospital, Minneapolis, April 23, aged 69, of acute anterior myocardial infarction.

Allison, Robert Seaman ✦ Salt Lake City; Rush Medical College, Chicago, 1904; fellow of the American College of Surgeons; served on the staff of St. Mark's Hospital; died May 21, aged 79, of heart disease.

Ankley, Jerome W. ✦ Grosse Pointe Park, Mich.; Detroit College of Medicine and Surgery, 1920; associated with St. John and East Side hospitals, and the Detroit Memorial Hospital in Detroit, where he died April 27, aged 60, of hypertensive heart disease and cerebral hemorrhage.

Arnette, Clarence Larry Edward, Alexandria, Va.; Medical College of Virginia, Richmond, 1933; member of the Medical Society of Virginia; past-president of the alumni association of his alma mater; member and past-president of the staff of the Alexandria Hospital; associated with the Circle Terrace Hospital, where he died May 12, aged 51, of brain tumor.

Asnis, Eugene Jacob, Woodbury, N. J.; Medico-Chirurgical College of Philadelphia, 1898; died in East Greenwich Township March 7, aged 78, of congestive heart disease and arteriosclerotic heart disease.

Bagby, John Robert ✦ Pulaski, Va.; University of Maryland School of Medicine, Baltimore, 1893; served as health officer of the Port of Newport News; died in the Pulaski Hospital March 21, aged 88, of cerebral hemorrhage and arteriosclerosis.

Baggerly, Walter E. ✦ Montrose, Mo.; University Medical College of Kansas City, Mo., 1907; died March 7, aged 74, of heart disease.

Banks, George Augustus, Wellsville, Ohio; Meharry Medical College, Nashville, Tenn., 1912; for many years practiced in Wheeling, W. Va.; died April 24, aged 72, of cerebrovascular accident.

Bardes, Albert Charles, New York City; Bellevue Hospital Medical College, New York City, 1893; died in St. Luke's Hospital April 18, aged 87, of arteriosclerosis.

Barr, John Walter, Mill Creek, Pa.; Jefferson Medical College of Philadelphia, 1905; an associate member of the American Medical Association; veteran of World War I; consultant in dermatology at the Conemaugh Valley Memorial Hospital in Johnstown, where he was chief of dermatology from 1922 to 1942, when he retired; died in the Veterans Administration Hospital, Altoona, May 1, aged 78, of encephalomalacia and arteriosclerosis.

Beardsley, John Frederick ✦ Frankfort, Ind.; Hahnemann Medical College and Hospital of Philadelphia, 1946; interned at the Indianapolis City Hospital; on the staff of the Clinton County Hospital, where he died May 5, aged 35, of diabetes mellitus.

Behn, Claud William ✦ Detroit; University of Michigan Medical School, Ann Arbor, 1921; member of the American Academy of Dermatology and Syphilology; held positions in dermatology at Woman's, Harper, Michigan Mutual, and old St. Mary's hospitals; died May 12, aged 61, of cerebral thrombosis.

Bingham, Junius Warren, West Plains, Mo.; Marion–Sims College of Medicine, St. Louis, 1898; died April 13, aged 86.

Bonus, Harrietta Margarete, Chicago; Loyola University School of Medicine, Chicago, 1928; died May 8, aged 57, of a heart attack.

Garner, Casper Elbert, Richland Center, Wis.; Milwaukee Medical College, 1906; died April 29, aged 76, of cancer.

Garren, Robert Hall ✦ Monroe, N. C.; University of Nashville (Tenn.) Medical Department, 1900; member of the staff of the Union Memorial Hospital; died in the Ellen Fitzgerald Hospital April 21, aged 84, of coronary occlusion.

Gaston, Stobo Rosebourgh, Travelers Rest, S. C.; Medical College of the State of South Carolina, Charleston, 1928; owner of a hospital bearing his name; died April 3, aged 56.

Gibson, Ira Malcolm ✦ Valdosta, Ga.; University of Chicago, The School of Medicine, 1941; served on the faculty of the Emory University School of Medicine, Atlanta; died in the Pineview General Hospital March 31, aged 47, of coronary disease.

Gillis, George Hiram ✦ Wiconisco, Pa.; University of Pittsburgh School of Medicine, 1910; died in Harrisburg April 18, aged 73.

Gleason, Notery Arthur ✦ Flint, Mich.; Detroit College of Medicine and Surgery, 1926; member of the American Academy of Dermatology and Syphilology; associated with Hurley and McLaren hospitals, and St. Joseph's Hospital, where he died April 4, aged 58, of bronchogenic cancer.

Godbold, Percy Ellis ✦ Pine Hill, Ala.; Atlanta College of Physicians and Surgeons, 1902; died in Selma April 3, aged 77, of cancer.

Haberfeld, Fritz Frederick, New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1936; member of the Medical Society of the State of New York; veteran of World War II; died April 2, aged 52, of coronary thrombosis and coronary arteriosclerosis.

Hallinger, Earl Stephen, Haddonfield, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1903; an associate member of the American Medical Association; formerly secretary of the New Jersey Board of Medical Examiners; fellow of the American College of Surgeons; on the emeritus staff, West Jersey Hospital in Camden, where he died May 7, aged 77, of cerebral vascular accident with pneumonia.

Hamilton, Ralph Emerson, Douglasville, Ga.; Emory University School of Medicine, Atlanta, 1916; member of the Medical Association of Georgia; died March 30, aged 65, of coronary infarction.

Havlicek, Theodore Leo, Portland, Ore.; Creighton University School of Medicine, Omaha, 1928; service member of the American Medical Association; member of the American Trudeau Society; veteran of World War II; associated with the Veterans Administration; died May 4, aged 54.

Haylett, Howard Bulkeley ✦ East Hartford, Conn.; University of Vermont College of Medicine, Burlington, 1907; on the consulting staff, Hartford (Conn.) Hospital, where he died May 1, aged 72, of congestive heart failure.

Hazel, James Kevin ✦ Hayden, Ariz.; University of Michigan Medical School, Ann Arbor, 1925; veteran of World Wars I and II; died April 21, aged 61, of coronary thrombosis.

Heatley, Joseph Lawrence ✦ Pittsburgh; University of Pittsburgh School of Medicine, 1930; fellow of the American College of Surgeons; also a graduate in pharmacy; on the courtesy staff, Homestead (Pa.) Hospital; died April 23, aged 53, of heart failure.

Heffering, Russell Joseph ✦ White Plains, N. Y.; University of Toronto Faculty of Medicine, Toronto, Ontario, Canada, 1927; for many years physician to the White Plains High School athletes; fellow of the American College of Surgeons; associated with White Plains Hospital; died in Mount Vernon May 7, aged 60.

Heidt, George Frank ✦ Charleston, S. C.; Medical College of the State of South Carolina, Charleston, 1915; also a graduate in pharmacy; died May 2, aged 66.

Henderson, Frank Harold ✦ Bloomington, Ill.; Hering Medical College, Chicago, 1905; associated with Mennonite Hospital and St. Joseph's Hospital, where he died April 16, aged 76, of a cerebral vascular accident and hypertension.

Hillegass, Victor Ellsworth ✦ Akron, Ohio; Ohio State University College of Medicine, Columbus, 1940; member of the American Academy of General Practice; veteran of World War II; died in the Akron General Hospital April 12, aged 44.

Hollander, John David ✦ Ripon, Calif.; Chicago Medical School, 1943; veteran of World War II; associated with the Memorial and City hospitals, Modesto; member of the American Academy of General Practice; died April 30, aged 42, of coronary disease.

Hulles, Edward, New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1907; died in the Metropolitan Hospital April 7, aged 74, of congestive cardiac failure and arteriosclerosis.

Hux, William Jackson, Essex, Mo.; Vanderbilt University School of Medicine, Nashville, Tenn., 1912; member of the Missouri State Medical Association; past-president of the Stoddard County Medical Society; past-president of the Bank of Essex; associated with the Missouri Delta Community Hospital, Sikeston, and the Brandon Hospital in Poplar Bluff, where he died April 22, aged 68.

Iorio, Michele, New York City; Regia Universitá di Napolia Facoltà di Medicina e Chirurgia, Italy, 1923; died in the Fordham Hospital April 5, aged 63, of duodenal ulcer with hemorrhage.

Irwin, Wilfred James Hunter ✦ Niagara Falls, N. Y.; University of Toronto Faculty of Medicine, Toronto, Ontario, Canada, 1924; served with the Royal Canadian Air Force during World War I; died April 27, aged 61.

Jackson, Arthur Page Jr. ✦ Denver; University of Colorado School of Medicine, Denver, 1932; member of the Radiological Society of North America; associated with St. Luke's Hospital; died in Idaho Springs, Colo., March 21, aged 49, of cancer of the tongue.

Jackson, Jesse Lee ✦ Indianapolis; Indiana University School of Medicine, Indianapolis, 1914; associated with Methodist, General, St. Vincent's, and St. Francis hospitals; died April 21, aged 71, of acute myocardial infarction and arteriosclerotic heart disease.

Jensen, Viggo Wilhelm, New Smyrna Beach, Fla.; Rush Medical College, Chicago, 1920; formerly on the staff of the Shelby Community Hospital in Shelby, Mich.; died April 22, aged 70, of cancer and cerebral hemorrhage.

Johnson, Jeremiah Robert, Elkin, N. C.; Medical College of Virginia, Richmond, 1927; died April 11, aged 65, of pulmonary hemorrhage.

Kemper, William Winton, Lancaster, Ohio; Medical College of Indiana, Indianapolis, 1903; died April 17, aged 79, of acute cardiac dilatation.

LaDue, Charles Nance ✦ Dallas, Texas; University of Texas School of Medicine, Galveston, 1938; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; veteran of World War II; clinical instructor of internal medicine at the Southwestern Medical School of the University of Texas; associated with the Methodist and Baylor University hospitals; died May 1, aged 43, of cerebral hemorrhage.

Larrabee, Charles William, Bradenton, Fla.; Eastern University School of Medicine, Baltimore, 1913; an associate member of the American Medical Association; medical director and part owner of the Bradenton General Hospital where he died April 13, aged 86, of pneumonia.

Larrabee, Herbert Manson ✦ Lowell, Mass.; Medical School of Maine, Portland, 1901; member of the American Psychiatric Association; served as school physician in Tewksbury, where he was associated with the Tewksbury State Hospital; on the staffs of St. John's and St. Joseph's hospitals; died April 28, aged 77, of heart disease.

Larson, Anders D., Los Angeles; University of Minnesota College of Medicine and Surgery, Minneapolis, 1893; died April 20, aged 94.

Larson, Oscar Franklin ✦ Machias, Maine; Albany (N. Y.) Medical College, 1905; veteran of World War I; past-president of the Maine Medical Association, Washington County Medical Society, and the Maine Medico–Legal Society; served as county medical examiner; formerly associated with the U. S. Public Health Service; died April 10, aged 76.

Lasswell, Bert James, Cromberg, Calif.; California Medical College, San Francisco, 1901; served as health officer of Plumas County; veteran of the Spanish–American War and World War I; died April 4, aged 80, of carcinoma.

Ledbetter, John Nelson, Clearwater, Fla.; St. Louis College of Physicians and Surgeons, 1896; died in the Morton Plant Hospital March 21, aged 84, of a cerebral vascular accident.

Lee, Edward Kerk, Newburgh, N. Y.; Harvard Medical School, Boston, 1915; member of the Medical Society of the State of New York; veteran of World War I; served in the regular U. S. Navy; died April 1, aged 68.

Leemhuis, Glenn H., Aitkin, Minn.; University of Minnesota Medical School, Minneapolis, 1936; died April 10, aged 44, of cerebral hemorrhage.

Little, Otis Williamson ✱ Abilene, Texas; University of Louisville (Ky.) Medical Department, 1911; member of the American Academy of General Practice; died in the Hendrick Memorial Hospital March 10, aged 77.

Loewenberg, Walter, New York City; Friedrich–Wilhelms–Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1919; member of the American College of Gastroenterology; on the staff of the Lenox Hill Hospital; died in Ormond Beach, Fla., March 31, aged 64, of coronary occlusion.

Lombardi, Generoso, Brooklyn; Regia Universitá di Napoli Facoltá di Medicina e Chirurgia, Italy, 1921; served on the staffs of the Brooklyn Doctors, Methodist, and Samaritan hospitals; died April 24, aged 61, of cerebral hemorrhage.

Long, Henry E., Wyoming, N. Y.; University of Buffalo School of Medicine, 1894; practiced in Buffalo, where he was associated with Millard Fillmore, Deaconess, and Buffalo General hospitals; died in the Wyoming County Hospital in Warsaw April 8, aged 88, of pneumonia.

Long, William Henry, Philadelphia; Jefferson Medical College of Philadelphia, 1896; an associate member of the American Medical Association; for many years attending physician at St. John's Orphan Asylum and physician at St. Edmond's Home for Crippled Children; served as director of St. Mary's Home for the Blind in Lansdale; for many years associated with the Misericordia Hospital; died April 17, aged 86.

Looney, Ormand Edgar, Paducah, Texas; College of Physicians and Surgeons, Dallas, 1908; died in Dublin April 19, aged 77.

Lyday, William Hall, Greenville, S. C.; Atlanta Medical College, 1914; member of the South Carolina Medical Association; veteran of World War I; on the staff of the Greenville General Hospital; died May 3, aged 66, of coronary occlusion.

McCain, James Price, Pittsburgh; Howard University College of Medicine, Washington, D. C., 1918; died in the Pittsburgh Hospital April 26, aged 65, of postoperative shock and carcinomatosis.

McClure, Herbert Arant, Mayo, Fla.; Atlanta Medical College, 1915; member of the Medical Association of the State of Alabama and the Florida Medical Association; veteran of World War I; served as district health officer of the Florida State Board of Health; at various times health officer of Winston, Choctaw, and Lamar counties in Alabama; died March 21, aged 70, of cerebral hemorrhage and hypertension.

McGeorge, Charles Samuel, Negley, Ohio; Western Pennsylvania Medical College, Pittsburgh, 1900; member of the Medical Society of the State of Pennsylvania; an associate member of the American Medical Association; on the board of trustees, First National Bank of Ambridge; served as president of the staff, Sewickley (Pa.) Valley Hospital, where he died May 4, aged 82, of cerebral thrombosis.

McKenna, Hugh ✱ Chicago; Rush Medical College, Chicago, 1903; associate professor emeritus of surgery at Northwestern University Medical School; member of the American Surgical Association; fellow of the American College of Surgeons; associated with St. Joseph Hospital; died May 12, aged 82, of coronary thrombosis.

McMahon, Edmund Stephen ✱ Butte, Mont.; Creighton University School of Medicine, Omaha, 1923; past-president of the Silver Bow County Medical Society; member of the staff of Community hospital; member and past-president of the staff, St. James Hospital; died March 27, aged 58, of carcinoma of the stomach.

Maner, William Albert, Atlanta, Ga.; Atlanta College of Physicians and Surgeons, 1901; died March 4, aged 82, of arteriosclerosis and hypertensive cardiovascular disease.

March, Samuel Franklin ✱ Carrollton, Ill.; University of Missouri School of Medicine, Columbia, 1909; served on the board of education and board of health; on the staff of the Thomas H. Boyd Memorial Hospital; died in Jacksonville April 28, aged 74, of bronchopneumonia.

Martin, Mabel Agnes, Binghamton, N. Y.; Cornell University Medical College, New York City, 1912; an associate member of the American Medical Association; past-president and vice-president of the Broome County Medical Society; for many years on the staff of the City Hospital; died April 21, aged 75, of heart disease.

Martin, Robert Vincent ✱ Savannah, Ga.; Medical College of South Carolina, Charleston, 1904; an honorary member and past-president of the Georgia Medical Society; served as a medical officer in the Mexican Border campaign; died April 15, aged 80.

Mason, Edward Charles, Oklahoma City, Okla.; University of Cincinnati College of Medicine, 1920; professor of physiology at the University of Oklahoma School of Medicine; fellow of the American College of Physicians; at one time fellow in medicine and first assistant in one of the sections on medicine, Mayo Foundation in Rochester, Minn.; died in the University Hospital, March 5, aged 65.

Mendelsohn, Bernard, Brooklyn; Long Island College of Medicine, Brooklyn, 1936; died in the Kings County Hospital April 13, aged 46, of hypertensive cardiovascular disease.

Millis, Robert Jordan ✱ Crawfordsville, Ind.; Indiana University School of Medicine, Indianapolis, 1921; veteran of World War II; served as county health officer and as a member of the board of education; died April 10, aged 59.

Moore, Cliff ✱ Lindale, Ga.; Birmingham Medical College, 1913; on the staffs of the Floyd Hospital and the McCall Hospital in Rome, where he died April 26, aged 71, of gastrointestinal hemorrhage.

Morrison, James Francis, Brooklyn; Johns Hopkins University School of Medicine, Baltimore, 1904; an associate member of the American Medical Association; in 1929 assistant sanitary superintendent of Brooklyn; served on the staff of Kings County Hospital; died March 23, aged 85, of cerebral hemorrhage and arteriosclerosis.

Morrissey, John Henry, New York City; Harvard Medical School, Boston, 1914; member of the Medical Society of the State of New York and the American Urological Association; secretary, Section on Urology, 1934-1935, and chairman, 1935-1936, American Medical Association; specialist certified by the American Board of Urology; on the staffs of the New York and St. Clare's hospitals; died April 5, aged 68, of congestive heart failure.

Murray, Arthur Thomas, Nineveh, Pa.; University of Pittsburgh School of Medicine, 1908; served as county health director; on the staff of the Greene County Memorial Hospital, Greensburg; died March 29, aged 76, of portal cirrhosis.

Murray, George Stewart ✦ Columbus, Ga.; University of Edinburgh Faculty of Medicine, Scotland, 1901; served in the British Army during World War I; formerly chairman of the staff, City Hospital; member of the Columbus Board of Public Safety; past-president of the Columbus Rotary Club; died March 31, aged 78, of urinary tract infection due to hemiplegia, cerebral arteriosclerosis, and heart failure.

Mutchler, H. Raymond, Dover, N. J.; College of Physicians and Surgeons, Baltimore, 1911; served as county physician, police commissioner, and alderman; on the courtesy staff, Dover General Hospital; died March 30, aged 69, of acute pulmonary edema.

Norman, Frank H., Waynesboro, Tenn.; University of Tennessee Medical Department, Nashville, 1901; died Jan. 22, aged 85.

Padget, Samuel ✦ Philadelphia; Universitatea din Iasi Facultatea de Medicină, Rumania, 1925; for many years on the staff of Albert Einstein Medical Center, Southern Division, where he died May 4, aged 66, of acute myocardial infarction.

Parker, Burton D., Grosse Ile, Mich.; Michigan College of Medicine and Surgery, Detroit, 1897; veteran of the Spanish American War and World War I; for many years on the staff of the Grace Hospital, where he died March 27, aged 80, of coronary thrombosis, arteriosclerotic heart disease, and prostatic hypertrophy.

Parmley, Tim Hennessey ✦ Electra, Texas; Memphis (Tenn.) Hospital Medical College, 1912; died April 15, aged 73, of injuries received in an automobile accident.

Parsons, John Eugene ✦ Little Rock, Ark.; University of Arkansas School of Medicine, Little Rock, 1933; served on the staff of St. Vincents Hospital; died in Hot Springs March 25, aged 49, of acute coronary occlusion.

Pascoe, Charles Samuel ✦ Tacoma, Wash.; University of Michigan Medical School, Ann Arbor, 1915; member of the American Urological Association; on the staff of the Tacoma General Hospital; died April 22, aged 65, of coronary disease.

Patterson, Wilfred Peter ✦ Grand Rapids, Mich.; Western University Faculty of Medicine, London, Ontario, Canada, 1921; on the staff of the Blodgett Memorial Hospital, where he died April 8, aged 59, of myocardial infarction.

Petersen, Fenton Joseph ✦ Richmond Heights, Mo.; St. Louis University School of Medicine, 1928; member of the American Academy of General Practice; health commissioner of Richmond Heights; veteran of World War II; associated with Incarnate Word Hospital and St. Mary's Hospital in St. Louis, where he died April 12, aged 55, of cerebral hemorrhage.

Petter, Reginald S., Beverly Hills, Calif.; University of Southern California College of Medicine, Los Angeles, 1902; an associate member of the American Medical Association; died in St. John's Hospital, Santa Monica, April 5, aged 78, of a heart attack.

Pfeffer, Edward Nicholas ✦ Milwaukee; Chicago College of Medicine and Surgery, 1914; a member of the city health department staff; died in the Milwaukee Hospital April 9, aged 66, of arteriosclerotic heart disease.

Pitz, Henry Robert, Kalamazoo, Mich.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1906; formerly on the staffs of the Bronson Methodist Hospital and the Borgess Hospital, where he died March 28, aged 77, of cerebral vascular accident, hepatic cirrhosis, and arteriosclerotic heart disease.

Pitz, Matthias N. ✦ Neenah, Wis.; Marquette University School of Medicine, Milwaukee, 1913; died in the Theda Clark Hospital Feb. 8, aged 73, of intestinal hemorrhage.

Podesta, Joseph S. ✦ Cincinnati; Medical College of Ohio, Cincinnati, 1901; veteran of World War I; died April 25, aged 80, of acute coronary thrombosis.

Podgur, Maxwell Philip ✦ New York City; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1902; veteran of World War I; died April 13, aged 75, of cerebral hemorrhage and arteriosclerosis.

Pond, Gilbert Palmer, Oak Park, Ill.; Rush Medical College, Chicago, 1920; served as health commissioner; veteran of World Wars I and II; on the executive board of the West Suburban Hospital, where he died May 20, aged 63, of generalized peritonitis.

Poole, Frank Augustus ✦ Saginaw, Mich.; Medical College of Ohio, Cincinnati, 1897; formerly city health officer; served as director of industrial hygiene for the Michigan State Department of Health; on the honorary staff of St. Mary Hospital, where he died April 25, aged 86.

Posner, Bernard ✦ Brooklyn; Chicago Medical School, 1948; member of the American Academy of General Practice; died in the Beth-El Hospital April 24, aged 40, of arteriosclerotic heart disease and hypertension.

Pullen, Guy Foote, Leonia, N. J.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1922; veteran of World War I; died April 1, aged 60.

Saunders, Roy Farra ✦ Fort Worth, Texas; Fort Worth School of Medicine, Medical Department of Fort Worth University, 1905; fellow of the American College of Surgeons; on the staff of St. Joseph's Hospital; died March 30, aged 77.

FOREIGN LETTERS

BRAZIL

BCG Vaccine.—Dr. Pedral Sampaio and Brazilian co-workers reported in *Temas de Leprologia*, an Argentine medical magazine, their experience with orally given BCG vaccine. Patients who suffered from dermatoses and who were hyperergic to tuberculin were given BCG vaccine by mouth. Their cutaneous lesions disappeared, and their general health improved. The behavior of the lepromin test in tuberculous patients was studied in 57 patients suffering from active pulmonary tuberculosis in the various stages. These patients were hospitalized in Hospital "Clemente Ferreira," Liga Paulist a Contra a Tuberculose in São Paulo. All but six were given a tuberculin test with 0.001 and 0.01 cu mm. of tuberculin. Of these, 38 (75.7%) had an allergic reaction. The lepromin test was made after the tuberculin reaction. The results obtained on the 30th day were as follows: the diameter of the papule was 5 mm. or more in 33 controls, less than 5 mm. in 22, and negative in 2 patients. Those whose papules were less than 5 mm. in diameter were given one to three doses of BCG vaccine by mouth at seven-day intervals. An increase in the diameter of the papule was evident in the patients vaccinated with BCG, while a decrease was shown by the nonvaccinated controls. A correlation between the reactions to lepromin and tuberculin and sedimentation rate, age, sex, color, and extent of tuberculous lesions was observed.

Strongyloidiasis.—Strongyloidiasis may be fatal. An example of the seriousness of this infestation was reported by O. Arantes Pereira and co-workers (*Rev. brasil. gastroenterol.* **8:** 345, 1956). Subacute duodenal obstruction occurred in their patient. The authors believe that strongyloidiasis could have caused a widespread inflammatory reaction of the mucosa of the second portion of the duodenum. The adult female parasites, larvae, and eggs may invade the mucosa and submucosa, but this rarely occurs. In addition, vascular or possibly nervous lesions could have been responsible for the spasm in this region. The authors, therefore, believe that strongyloidiasis played an important role in the obstruction of the duodenum, which was the cause of death in their patient, and that the infection requires more accurate clinical and pathological studies for the correct interpretation of its etiological and pathogenic aspects.

Esophageal Stricture.—In the management of the esophageal stricture caused by swallowing lye, Dr. Matos Barreto introduces one esophagoscope through the mouth and another through a gastric stoma as soon after the injury as possible. Thoracotomy is performed, and the esophagus exposed. The arch of the azygos vein may have to be cut between ligatures. The exterior of the esophagus is made visible by means of a mirror used by the endoscopist who handles the retrograde instrument. The upper and lower portions of the esophagus are brought into the same axis, and the distal ends of the two esophagoscopes are approximated as closely as possible. A long cannula is introduced through the retrograde scope and advanced into the narrowed portion of the esophagus below the stricture. The surgeon slides the esophagus over the cannula as far as possible. A long threaded needle is introduced through the cannula and thrust through the constricted portion of the esophagus into the upper esophagoscope. Threads brought out through a nostril and the gastric stoma are used as a guide to dilators. Excellent results are reported.

Megacolon and Megaesophagus.—The pathogenesis of congenital megacolon is completely different from that of acquired megacolon, according to F. Köberle (*Rev. goiana med.* **2:**100, 1956). Dilations of hollow viscera may result from injury of the intramural plexuses by Trypanosoma cruzi. The achalasia of the sphincter which may result from such a lesion is a secondary, not a determining, factor, since dilatations may be produced in segments of the digestive tract that have no sphincter. The principal factor is in alteration of the motility of the organ due to the destruction of the nervous tissue of the muscular wall, leading, in the initial phase, to hypertrophy and hypertonia of the wall. This phase progresses to the enlargement and complete atony of the organ. Serial sections from 7 patients with megaesophagus and 14 with American trypanosomiasis gave evidence that megaesophagus is a manifestation of this disease. Transfer of the parasites in the esophageal muscle layer leads, after rupture of the pseudocysts, to a granulomatous inflammation in the interior of the muscle layer and, due to lymphogenic spread, to destruction of the nervous plexus and lack of coordination of the peristaltic movements and achalasia of the sphincter. This results in dilatation of the esophagus. A similar mechanism produces megacolon and other similar processes in hollow viscera.

FRANCE

Hormonal Treatment of Rheumatic Fever.—Mozziconacci and Caramanian (*Semaine hôp. Paris* **33:**288, 1957) report the results of hormonal treatment of rheumatic endocarditis in 387 patients (207 with initial attacks) followed up for six months to six years. These patients had been treated with doses of hormones ranging from 100 to 300 mg. The dose had been increased when found to be inadequate, and treatment was continued until the sedimentation rate fell to less than 20 mm. per hour. The authors recommend that hormonal treatment be followed by treatment with aspirin in effective doses for 2 or 3 weeks. With this treatment 75% of the patients with severe cardiac rheumatism had survived. Those with moderate cardiac rheumatism had im-

The items in these letters are contributed by regular correspondents in the various foreign countries.

proved by 29% and those with initial attacks by 50%. Of those with no cardiac involvement, 96% had recovered without valvular sequelae. These results were better than those in which smaller doses of hormones or aspirin alone were used.

Aspirin Treatment of Rheumatic Fever.—Mozziconacci and Manuel (*Semaine hôp. Paris* 33:296, 1957) state that aspirin is effective in the treatment of rheumatic fever only if adequate doses are used. Salicylate derivatives are absorbed into the blood rapidly, but a large proportion of the blood salicylate remains inactive because it is protein bound. As the salicylate level rises, the salicylate clearance rate is increased, so that, when repeated doses are given, the result is not a gradual accumulation but a salicylemia "en plateau." Aspirin undergoes a hydrolysis that gives it a delayed action. This makes it possible to obtain high salicylate levels with doses smaller than those required when using other salicylates. The treatment is effective when the salicylemia plateau approaches 30 to 35 mg. per 100 cc. When the level reaches 35 to 40 mg. per 100 cc., there is evidence of poisoning. The passing from an effective to a toxic level generally corresponds to the moment when the renal adaptation power fails. Rapid salicylate clearance is reestablished as soon as the drug is withdrawn. Alkalinization of the urine with sodium bicarbonate may double the renal clearance of the salicylate by blocking tubular reabsorption. The action of aspirin on exacerbations of rheumatic fever compares favorably with that of cortisone if adequate doses are used, except that the decrease of the sedimentation rate is less rapid. Aspirin is still the drug of choice if hormonal treatment is contraindicated.

Psychic Complications in Children Treated with Hormones.—Mozziconacci and co-workers (*Semaine hôp. Paris* 33:308, 1957) observed 57 children treated with corticotropin and cortisone and found that these hormones rarely cause severe reactions but may result in disturbances in the appetite and sleep. Euphoria is seen less often than in adults. Depression, on the other hand, was a common reaction in children. Next came anxiety and agitation, hypomanic episodes, manic excitation, and visual disorders. In only two patients were severe disturbances observed. One showed delusions of persecution and the other serious intellectual deterioration. The authors concluded that, although hormonal treatments benefited patients with many somatic diseases, the advantages should be weighed against the risk and that such treatment should not be continued in patients with evident hypercorticism, marked psychic manifestations, or changes in the electroencephalogram.

Prevention of Relapses in Rheumatic Fever.—J. Labesse and co-workers (*Semaine hôp. Paris* 33:323, 1957) observed 377 children with rheumatic fever, of whom 56.9% had cardiac involvement. They gave sulfadiazine, penicillin G orally, injections of benzathine penicillin G, and phenoxymethyl penicillin orally. The per cent of relapses per year was 2.8 (17 patients). This per cent fell to 0.8 (5 patients) when only those patients subjected to an accurate prophylactic program were taken into account. Comparatively, the per cent of relapses was 20.5 (56 patients) for the 167 children who interrupted the prophylactic regimen. The development of tonsillitis due to reinfection with Streptococcus pyogenes was observed in 5.2% of the children under the prophylactic regimen and in 15.3% of those who had interrupted this program. Three (10%) of the patients with tonsillitis who were treated by curative doses of antibiotics had relapses, and 31 (53%) of those not so treated had relapses.

Persistence of Gonococcic Morbidity.—P. Durel (*Presse méd* 65:829, 1957) states that the incidence of gonococcic infections has not decreased in the last six or seven years in spite of the individual effectiveness of antibiotics. The detection of infected women is not easy, but the use of treatment that reduces the risk of reinfection should be beneficial individually as well as socially. This sort of protection may be obtained only by using long-acting penicillin. The objection to this treatment on the grounds that it may conceal a syphilitic infection contracted at the same time is unjustified. The author believes that the best treatment of gonorrhea in both women and men is a single injection of 1,200,000, or preferably 2,400,000, units of benzathine penicillin (with or without streptomycin). This form of penicillin, because it is long-acting, is likely to reduce the incidence of gonorrhea as well as that of syphilis.

Metabolite Balance in Cardiac Surgery.—G. Dubourg and co-workers (*Presse méd.* 65:845, 1957) in a series of dogs under general hypothermia undergoing direct vision intracardiac operations analyzed those metabolite imbalances that interfere with normal electric and mechanical regulation of the heart beat. They stressed the necessity for preventive rather than corrective measures. Hyperventilation, hyperoxygenation, and a neuroplegic premedicament are essential. It is advisable to give the subject a gradual potassium overcharge in the preclamping period and an adequate supply of glucose and calcium during the declamping stage. Ten of the 13 dogs on which this technique was used survived after performance of cardiotomy on the right.

INDIA

Chronic Splenomegaly.—A. K. Basu and co-workers (*Journal of the Indian Medical Association*, May 1, 1957) report that the cause of chronic splenomegaly in some patients cannot be determined even after detailed investigation. In many of these patients cirrhosis of liver with ascites or other evidence of portal hypertension eventually develops. The authors performed a splenectomy on many such patients. Splenectomy was also performed on a few patients in whom the cause of the splenomegaly was known. The preoperative investigations of all these patients included examination of blood and bone marrow, estimation of plasma proteins, liver function tests, and the taking of esophagograms and splenoportal venograms. The portal venous pressure was determined at operation and a liver

biopsy specimen taken. In 39 of the authors' series of 50 operative cases, no etiological factor was apparent. In 32 patients who had a history of intermittent fever with enlargement of the spleen, the residual splenomegaly had increased even after the cessation of the bouts of fever. Histological examination of these spleens did not show any specific lesion. In 15 patients with chronic uncomplicated splenomegaly there was no evidence of hepatic cirrhosis or portal hypertension. Splenectomy was performed because of continued ill-health and evidence of hypersplenia in some patients. The results may be considered satisfactory as judged by the improvement in the general health and blood findings. In the second group of 19 patients who had continued ill-health and evidence of hypersplenia as well as clinical evidence of cirrhosis and portal hypertension, splenectomy was also performed. Results were satisfactory in 11 and fair in 3. There was one operative death. In 10 patients, removal of the spleen caused regression of the portal hypertension. In five patients who also had nodular hyperplasia of the liver, liver function studies showed improvement after operation in spite of the fact that jaundice developed. In five patients, splenectomy was performed for extrahepatic obstruction of the portal venous system. There was no ascites or liver dysfunction in these patients.

Splenectomy was performed in two and was combined with splenorenal shunt in the remaining three. Except for one patient who died after operation, all were improved. In four patients with cirrhosis of liver but without significant splenomegaly, the spleen was removed because of portal hypertension and in order to exclude hypersplenia. One patient died after temporary improvement, and one was free from symptoms four years after operation. In two others, it was too early to evaluate the results. In one patient with visceral leishmaniasis, response to specific treatment was satisfactory only after removal of the spleen, which was the main reservoir of the organisms. One patient with Cooley's anemia showed improvement in blood findings only after splenectomy. Taken as a whole, hematological improvement was significant in 34 patients; liver function showed improvement in 22; and evidence of portal hypertension regressed in 18.

Acute Encephalitis.—Web and Pereira (*Indian J. Child Health* 6:5, 1957) state that acute encephalitis in children in South India was formerly always due to virus. Other agents, however may also cause acute encephalitis. The authors have therefore tried to lay down certain criteria for the diagnosis of viral encephalitis. These are (1) definite onset with fever; (2) marked involvement of the central nervous system, with drowsiness or coma; (3) bacteriologically negative spinal fluid with a normal or elevated cell count and normal or slightly increased protein and sugar concentrations; and (4) negative history and findings for such conditions as measles and vaccinia. Of 1,075 admissions in a period of 16 months, 39 patients satisfied these criteria, but various laboratory investigations on blood and electroencephalograms ruled out viral encephalitis in 10. Of the remaining 29, serologic studies for specific antibodies showed 18 of them to be Japanese B encephalitis, while specific antibodies to Japanese B, West Nile, Murray Valley, and Tamil Nad encephalitis viruses were not found in the remaining 11. Thus, in spite of definite diagnostic criteria the clinical diagnosis proved wrong in a fair number of patients.

Industrial Medicine.—At the fifth annual convention of the Society for the Study of Industrial Medicine in April, the chief minister stated that coordinated research on problems associated with industrial hygiene by all the agencies concerned would not only bring about industrial peace but would also help to raise industrial production. The president of the society said that the introduction of the Employees' State Insurance Scheme had created an impression in the minds of some industrialists that it was no longer the responsibility of employers to provide a factory medical service. Industrial medical service, however, plays a vital role in stepping up production. The employees, employers, and government should join in forming an industrial health service. Such a service presupposes an intensive postgraduate training course in industrial medicine and hygiene. This course of study should include, among other subjects, industrial psychology, industrial hygiene and sanitation, factory first-aid service, and safety measures. The main functions of the service should be preemployment examination, periodic examination of workers, preventive treatment, education and instruction in sanitary habits, and rehabilitation of the disabled.

Employment State Insurance Scheme.—Since the introduction of the Employment State Insurance Scheme in 1952, there has been a rapid extension of the scheme, with the result that it now covers 1,125,000 workers in 51 areas in 10 states. This constitutes about half the population working in factories covered under the act. Beneficiaries suffering from tuberculosis now get medical treatment for a period of 18 to 24 months from the time they have to leave employment. Cash benefits are also granted for a further period of 18 weeks. Artificial limbs are provided free of charge to insured persons who lose their limbs on the job. Medical care, which originally consisted of only outpatient services, now includes specialist treatment, ancillary investigations, and hospitalization on the scale of one general bed for 800 employees, one bed for tuberculosis cases for 1,600 employees, and one bed for maternity cases for 500 insured women. Wives of insured persons will be entitled to outpatient treatment and home obstetric care.

Hydrocortisone in Tuberculous Meningitis.—A. F. Golwalla and co-workers (*Indian Journal of Medical Sciences*, May, 1957) state that steroids have a definite place in the treatment of tuberculous meningitis. In addition to the routine specific therapy, steroids, when given orally or intramuscularly, cause rapid improvement in the general condition; reduce the incidence of spinal or ventricular block; release tubercle bacilli from fibrinous exudate, thus exposing them to the action of antituberculous drugs; and reduce the death rate from this disease. The authors gave hydrocortisone intrathecally to nine adults with tuberculous meningitis who had severe toxemia and increased intracranial tension. Streptomycin and isoniazid were also given.

The hydrocortisone was given in doses of 20 mg. on alternate days for the first 10 days and then twice a week for five more injections. Within a few days all patients showed marked improvement, and their eventual recovery was complete.

Carcinoma of the Male Breast.—M. V. Sirsat (*Indian Journal of Surgery*, April 1, 1957) reported 30 cases of carcinoma of the male breast seen in the period 1941 to 1955. In the same period, there were 1,596 cases of carcinoma of the female breast. The age of the patient varied from 35 to 80 years. About 35% of the patients came for treatment within six months after they first noticed a lump in the breast. In more than half the presenting symptom was ulceration of the nipple associated with either a mass in the breast or retraction of the nipple. The axillary lymph nodes were involved clinically in 20 patients, but histological examination showed metastases only in some of them. The right breast was involved in 15 patients, the left in 14, and one had bilateral involvement. Only one patient had gynecomastia preceding carcinoma. The lesion showed little difference from that of female breast carcinoma, but papillary cystadenocarcinoma occurred in 20% of the patients, this per cent being an unusually high incidence for this variety of carcinoma.

NORWAY

Centenary of the Leprosary in Bergen.—The century-old leprosary in Bergen burned to the ground on Christmas Eve, 1853. On June 12, 1857, the new building admitted its first patient. A century later, this building (the largest building in Norway) houses only 5 lepers, whereas more than 2,000 lepers have lived in it in the past. In *Tidsskrift for den norske Lægeforening* for May 15, Dr. R. Melsom traces its history and that of D. C. Danielssen and Armauer Hansen, men who have made history in the field of leprosy. Most of the lepers admitted to the hospital a century ago suffered from some skin disease, such as scabies, for which a bath, after the application of a tar ointment, was prescribed. Thereafter a bath once or twice a week for every patient became the rule. Occupational therapy was practiced early, the men being employed in making nets, carpentering, shoemaking, and working in the garden, while the women sewed, knitted, and spun. Danielssen, one-time director, was a keen pathologist whose eagerness for postmortem examinations was frowned on by his prospective subjects. His life was said to have been threatened on this score, but he continued performing autopsies and concluded that certain brown elements found in the tissue of lepers must be characteristic of the disease. These elements are now known to be macroscopic cultures of Mycobacterium leprae. When Virchow visited Bergen in 1859, and was shown these elements, he dismissed them as patches of fatty degeneration quite unconnected with leprosy. It remained to Hansen to discover the unstained M. leprae in 1873. In the following year, he reported his discovery to the medical society in Christiania (now Oslo). A little later, with the assistance of Weigert and Koch, Hansen succeeded in staining this bacillus. His attempts to transfer the bacillus from a patient with the nodular form of leprosy to a patient with the smooth form of the disease proved abortive and led to legal proceedings against him, ending in his dismissal from his appointment as the hospital's chief. He was, however, allowed to remain as Norway's chief leprosy medical officer till he died in 1912.

Ullevaal Hospital as a Research Center.—In an address given at the annual meeting of the Norwegian Council for Science and the Humanities, Carl Semb traced the evolution of the Oslo City Hospital, Ullevaal, as a research center with special facilities for experimental work (*Journal of the Oslo City Hospitals*, May, 1957). This hospital already has two research institutes, one of them, the University Institute for Respiratory Physiology, and the other, the University Institute for Experimental Medical Research. The former is primarily concerned with studies of the lungs and the pulmonary circulation, with special reference to the advancement of major thoracic operations. At this institute a new method for testing the total cardiopulmonary function was adopted, with continuous registration of the amount of total oxygen consumption and discharge of carbon dioxide during rest and exercise. These and other tests are of value in the 400 or more pulmonary operations performed yearly at the hospital. The Institute for Experimental Medical Research has been concerned with operations on the heart and blood vessels. Trials have been carried out with an artificial heart-lung machine that permits of exclusion of the heart and lungs during operations on the heart. Methods for direct measurements of the blood flow by the use of isotopes have been devised. A new surgical technique has been developed in connection with partial renal resection, and 266 such resections have been performed at the hospital on human subjects without any operative deaths. Work is progressing with the construction of an artificial kidney by which renal excretory function can be temporarily imitated in patients with transient renal failure. Another comparatively new branch is the neurosurgical department. The rapidly increasing demands of neurosurgery have already necessitated plans for a new wing to the surgical block to provide room for 70 beds for neurosurgical patients and for new operating rooms.

Mass Radiography, Tuberculin Testing, and BCG Vaccination.—Since 1943 there has been a great extension of mass radiography with tuberculin testing and BCG vaccination throughout Norway. By 1952, seven mass radiography teams, five on shore and two at sea, were at work, examining everyone over the age of 14 years. Since 1949, mass radiography has been combined with BCG vaccination of the persons found to be tuberculin negative. The Ministry of Health's tuberculosis department has an enormous task in coordinating this service, which requires not only 24 radiologists and specialists in the diseases of the lungs but also the aid of health officers throughout the country. This is why the latest report is for 1952. In that year,

308,153 persons underwent mass radiography. In 12,648 cases supplementary examinations were necessary. Changes in the lungs and pleurae were found about 10% more frequently in men than in women, whereas cardiovascular changes in all the age groups were more common among women (22 per 1,000) than among men (13.9 per 1,000). In 417, or 14.5 per 10,000, persons undergoing mass radiography, destructive lesions of pulmonary tuberculosis were found. Special interest attaches to the 30,534 persons who were known to have undergone BCG vaccination earlier. The morbid findings in mass radiography testing were comparatively rare in this group, the difference in favor of the vaccinated growing with the age of the persons examined. While only 16.3 per 1,000 BCG-vaccinated males who underwent radiography were referred to a supplementary examination because of radiographic findings, 43.1 per 1,000 of all the persons radiographically examined were so referred.

UNITED KINGDOM

Duodenal Ulcer Treated by Combined Gastroenterostomy and Vagotomy.—The treatment of 197 duodenal ulcers by vagotomy and posterior gastrojejunostomy is described by Hindmarsh (*Lancet* 1:1113, 1957). The most troublesome side-effects of vagotomy (flatulence, vomiting, and diarrhea) are avoided if adequate drainage is provided by a posterior jejunostomy creating a large stoma extending from the lesser to the greater curvature at the junction of the body with the antrum. Adequate drainage of the latter is essential. A complication of the operation is gastric stasis, which may last several days. This is avoided by discontinuing aspiration as soon as possible, usually within 24 hours after the operation, and the prompt feeding of semisolids by mouth by the third postoperative day. The giving of solid food stimulates gastric activity and promotes restoration of normal intestinal function. Hindmarsh has been treating duodenal ulcer by this method for eight years, and reports a satisfactory result in 98% of the patients so treated. The passage of time showed no reduction in the percentage of satisfactory results.

Radiobiology Unit.—In 1954, the British Empire Cancer Campaign received a donation of $700,000 to equip laboratories for the study of roentgen rays and other ionizing radiations on living tissues. These laboratories have now been opened at the Mount Vernon Hospital, London. Fundamental problems on the action of radiation on living cells will be studied—in particular, the early stages of irradiation damage preceding the microscopic changes. It is desired to study these early changes with a view to controlling the nature and extent of irradiation damage. One method used is to expose the cell to the total amount of radiation in the shortest possible time and to observe the chemical changes occurring in the cell or its components before and after exposure.

The unit has been specially designed for a 200,000-volt x-ray machine, which is housed in rooms with thick concrete walls, and an electron-pulse generator. Both these machines and the instruments measuring changes in the cells are operated from a control bay between them. The electron-pulse generator emits bursts of electrons at such a high intensity that cells in the path of the beam can be exposed to any desired amount of irradiation, up to a limit exceeding anything previously attained, in a single pulse lasting only about two-millionths of a second. Special methods will be used to examine the changes in the cell during and after exposure by means of flashes of light lasting only a few millionths of a second. These studies bear closely on the use of oxygen to increase the power of x-rays in the treatment of cancer, since oxygen is thought to augment radiation damage by entering into chemical reactions of extremely short duration. The Mount Vernon Hospital itself, which treats about 1,150 cancer patients a year, has an exceptionally well-equipped radiotherapy department fitted with a 4-million-volt x-ray machine and a cobalt-60 theratron.

Frozen-Tumor Bank.—At the Central Laboratories of the Imperial Cancer Research Fund, Dr. James Craigie has established a bank of transplantable tumors in the frozen state. This frozen-tumor bank is thought to be the only one of its kind and is intended to serve as a source of tumor tissue for research workers. The tumors are frozen for long-term storage. About 50 types of transplantable tumors are in storage, including strain-specific and non-strain-specific mouse tumors, a Jensen rat sarcoma, a Walker rat tumor, a Brown-Pearce rabbit tumor, radium-induced guinea pig tumors, and several fowl tumors. The variety of strain-specific mouse tumors is limited by the number of colonies of different strains of mice that are maintained in the laboratories, but it is hoped to add to them. Some types of tumor not in the bank are being studied in the fund's laboratories at Mill Hill, London.

Death Associated with Steroid-Hormone Therapy.—Allanby reported 18 deaths associated with steroid-hormone therapy (*Lancet* 1:1104, 1957). In 11 cases, steroid therapy was considered directly responsible for death and probably hastened death in 3 others. Infection caused at least six, and probably seven, of the deaths. This was attributed to the fact that hormone therapy suppressed or masked the symptoms and signs of infection. Gastrointestinal hemorrhage and perforation were each responsible for three deaths. Other causes of death were adrenal failure and rupture of the aorta, but only in the case of adrenal failure was steroid therapy suspected as a cause of death. Most treatments have their risks and it would be a great pity if the dangers of steroid therapy were overemphasized. It is unwise, however, to embark on steroid therapy without adequate means for careful and regular supervision of the patient and unless real benefit can be anticipated.

Radiation and Leukemia.—In 1955, the Medical Research Council appointed a committee to examine the hazards of nuclear and allied radiation. W. M. Court-Brown and Richard Doll were asked to undertake an extensive investigation of leukemia and aplas-

tic anemia occurring in patients who had ankylosing spondylitis and had undergone treatment by irradiation. Their report has now been published (Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis, M. R. C. Special Report, Series No. 295, H. M. S. O., 1957). The records of 13,352 patients from 81 radiotherapy centers were investigated and the patients carefully followed up. Seventy-two of the patients were found to have ankylosing spondylitis, aplastic anemia, or myelofibrosis; 49 of the records were among those taken from the hospital records, and 23 were from other sources. From national vital statistics the numbers of deaths that would have been expected in the 13,352 cases of ankylosing spondylitis were 2.9 for leukemia and 0.3 for aplastic anemia. Actually 28 deaths were reported as due to the former and 12 to the latter disease. The mortality from leukemia among patients with ankylosing spondylitis treated by irradiation is thus about 10 times that of the population at large. A possible explanation is that patients with ankylosing spondylitis are more likely to get leukemia than are healthy persons, irrespective of the method of treatment. Against this argument are the following observations. The distribution of the different cell types of leukemia in patients who have undergone treatment by irradiation is not the same as in untreated patients, in whom the incidence of lymphatic leukemia is higher. There is also a relation between the dosage of irradiation and the incidence of leukemia. This was considered by the authors to be strong evidence that irradiation is a cause of leukemia.

In spite of the careful analysis by Court-Brown and Doll, the nature of the relationship between radiation dosage and leukemia is not clearly defined, so that it is not possible to determine a maximum allowable dose of radiation. These investigators believe that there is no threshold dosage—a view based on the observation that the incidence increases with the dosage, except at the highest level. This is analogous to the induction of gene mutations by irradiation. Discussing the occurrence of leukemia among the Hiroshima survivors, the authors consider that the incidence of the disease is related to dosage of radiation in a linear manner. They admit, however, that much more work must be done before the true dose-response relationship between irradiation and leukemia is ascertained.

Tuberculosis in Lodging Houses.—In London, accommodation for the solitary male worker receiving a low wage varies from well-organized hostels to the worst type of flophouse. The best working-men's hostels are Rowton Houses, which, with the Salvation Army hostels, have 8,750 beds in London. Other lodging houses bring the number up to about 13,000. Dr. Kenneth Marsh, suspecting that lodging houses are reservoirs of tuberculosis, cooperated with the directors of local mass miniature radiography units in surveying the inmates. In five surveys, 1,200 men from lodging houses were x-rayed, and 47 were found with active tuberculosis. With 21 cases already known, this was an incidence of 56 cases per 1,000 persons. Of a further 211 men referred for examination from these houses, 47 were found needing treatment, and 50 others were already known to be tuberculous. In another group of 1,125 men sleeping in lodging houses, 26% of those between the ages of 35 and 44, 53% between the ages of 45 and 54, and 66.6% between the ages of 55 and 64 years showed radiographic evidence of tuberculosis. The incidence of tuberculosis found by mass radiography in the population at large in London was 5.8 per 1,000 in the 25-to-44-year age group and 11.2 in the 45-to-64-year age group.

In another survey, Marsh found eight men needing treatment for tuberculosis in a house where only 47 people were examined. The difficulty is to get the inmates of lodging houses to submit to examination. Marsh recommends that every person admitted to prison be x-rayed. This large reservoir of tuberculosis can be dealt with only by the cooperation of the medical profession and the various departments in local and national government that are concerned with health and welfare.

Congested Curriculum.—The British General Medical Council published a review of the medical curriculum and the *British Medical Journal* of June 8 has commented on this review. After passing preliminary examinations in general education, physics, chemistry, and biology, the medical student must still face a minimum period of professional study of five years. The council considered the possibility of reducing this minimum period, but decided that the time was not opportune for this. It encouraged the extension of interdepartmental teaching throughout the whole period of professional study. The student is no longer required to dissect the whole body. In the section devoted to medicine, there is great stress on preventive medicine and on providing the student an opportunity to learn something of the work of the general practitioner. Although the student has still to spend not less than two months in residence while receiving clinical instruction in obstetrics, much of the detail formerly required has been dropped; he has to conduct only an adequate number of deliveries compared with the not less than 12 required in the old recommendation (1947). He should be given ample opportunity to attend clinicopathological conferences and should be acquainted with the principles governing the design and interpretation of clinical trials. As to examinations, the council now specifies 10 subjects, 5 less than 10 years ago, and has refrained from designating subjects in which separate examinations should be held.

"Smoking-Cure" Pills.—Mr. H. H. Bagnall, Birmingham city analyst, says of pills guaranteed to cure the smoking habit forever: "If willpower and resolution are not strong enough to break off the habit, I doubt very much if such tablets would do so." He found that the pills consisted of 0.4 Gm. of iron sulfate coated with sugar and colored. He concluded that there was no obvious reason why swallowing them by the dozen should have any effect on the smoking habit. If the pills are sucked, however, the unpleasant taste caused by the combination of smoke and iron sulfate might act as a deterrent, but too great indulgence in the pills should be avoided, as constipation and irritation of the stomach might follow.

CORRESPONDENCE

SKIN LESIONS

To the Editor:—I read with interest a recent editorial by A. J. Lehman, "The Cosmetic Problem" (*J. A. M. A.* **164**:416 [May 25] 1957). A desire was expressed for basic study to help solve the issue. It was considered more than a coincidence that adolescent pimples are also being referred to as the acne problem. I wonder if these two problems have something in common. Bad complexions are burdened with advice and loads of directions for treatment; but, in spite of knowing so much about what to do, some 50% of youthful males and females have pimply faces. Adding a disconcerting note is the fact that teen-agers from the homes of physicians contribute more than their share to the incidence.

It seems that, in the rush to do something, the psychology of adolescense has been overlooked. As sure as puberty comes about, there occurs a time when both sexes seek to improve and adorn each and every physical attribute to the highest state of perfection. Hair styling is practiced with much fervor. What parent has not noticed the lengthening intervals spent in the bathroom, the unaccounted-for delay in being ready for school, sudden attention to cleanliness, and furtive glances at mirrors to make sure that each beauty feature is the way it should be. It is at this stage of development that there starts on the maturing skin a concerted effort to better it. From every bar and jar, a full measure of beauty is wanted. There is present an urgency to try to confirm the most outlandish cosmetic advertising.

About this same time, youngsters come out of the bathroom with the face reddened and irritated, and a few wheals point to the squeezing practice. At once, there is offered endless advice. Everybody knows what to do, and, as likely as not, the youngster is accused of being dirty. The parent or relative may take a hand in the washing. A brush may be purchased. As the irritation becomes more complex, relief is sought from cosmetics and medicaments. Finally, putting things on and taking them off becomes a ritual whose outcome is erythematous acne, noted for bleeding points, oiliness, and massed comedones. These teen-agers with their faces like balls of fire are now the end-stage of always doing something. They epitomize too much advice, care, and treatment.

Several recent experiences point to the importance of psychological factors in the course of acne.

A young executive, aged 22, was seen for a dermatitis on the leg. The residual of a severe acne was noticed. All during high school and college, the acne had remained severe and acute. Treatments were unsuccessful. His present position demanded the most of him. He married; they decided to help build their home, with the result that every spare moment was occupied. Casually, he remarked, "You know I didn't have time to look after my skin," and now his facial expression brightened, "Up to this time, it never dawned on me that that is why it got better."

A white male, aged 24, presented a grade 4 acne with extensive keloid formation, especially on the chest. It was of eight years' duration. A bentonite lotion was prescribed. This was to be patted on the affected areas at night and rinsed off with warm water in the morning. Soap was forbidden as well as washcloths. The skin was to be patted dry, not rubbed. In addition, he was informed that all manipulative acts must cease if he wanted to get well. At the end of three weeks, an unbelievable change had occurred. The face had lost its greasy redness, and there were no active lesions. Breaking habits is difficult, and this patient was asked for the secret. He responded with two reasons. When he stopped using soap and washcloths, the irritation of the skin lessened so he did not have to touch or press it; and he was getting married in three months and wanted his skin to look nice. The marriage impulse in this patient transcended all other motives and habits.

A housewife, aged 24, with two children was seen for a pustular acne of six years' duration, affecting the chin and sides of the face. This had become acute the previous three months. During a period of nine weeks, several treatment procedures were outlined. There was no improvement, and every visit she asked, "Can't you do something more for me?" Finally, in desperation, she was asked what she would like to do. To my surprise, she wanted a typewriter. The husband was called from the waiting room, and he said he would buy two typewriters if it would help. I insisted that she let me see her first four lessons. These were brought over on the next visit, and during the following two weeks all acute acne lesions had disappeared. Restless fingers manipulated the typewriter instead of the face.

If basic study is directed at the cosmetic problem, the faces of our teen-agers will be less irritated. This achievement alone will lessen the acne problem.

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TREATMENT FOR DIABETES MELLITUS

To the Editor:—It has been two years since the introduction of tolbutamide (Orinase) in the United States. Many of us have had excellent results from its use. All observers agree that it is effective in the obese, elderly patient with mild diabetes and that it is a valuable contribution in the treatment of diabetes mellitus, points which were well covered in the excellent editorial that appeared in the June 1, 1957, issue of The Journal. However, I feel that a completely incorrect impression that the orally given hypoglycemic agents are insulin substitutes is created by such articles as "Clinical Use of Tolbutamide (Orinase) in Office and Home Care of Diabetics" in the June 8, 1957, issue of The Journal. I must express my objection especially to the statement, "No longer do their

[diabetics'] lives depend upon a refrigerator's proximity—a liberation of marked psychological importance." Furthermore, 45 cases is a grossly inadequate sample on which to compute the expected percentage of diabetics needing insulin.

It is important to bear in mind that in 50% of cases, the diabetes can be controlled by diet alone. Probably the condition of at least 80% of the obese, elderly patients with mild diabetes could be controlled by diet alone. Even in these cases insulin is the drug to be used rather than tolbutamide when infection or acute stress develops.

Orally given hypoglycemic agents are unpredictable, since it is only after trial and error that the suitable reactor can be found. They cannot be relied on solely, since under stress insulin is required. Their effectiveness is often short-lived, requiring later recourse to insulin. Side-reactions such as nausea and vomiting, abdominal pain, and vertigo are common enough not to be overlooked.

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LAW DEPARTMENT

MEDICOLEGAL ABSTRACTS

Osteopathy: Injunction to Restrain Enforcement of Revocation Order.—This was an action by the petitioner, an osteopath, to restrain the State Board of Health of Kentucky from enforcing an order revoking the petitioner's license to practice osteopathy. From a judgment denying relief sought, the petitioner appealed to the Court of Appeals of Kentucky.

The petitioner was admitted to the practice of osteopathy in Missouri in 1922 and, in 1926, through reciprocity, was licensed to pursue the same profession in Kentucky. He admitted that he did not hold the degree of Doctor of Medicine, that he had no right to use the professional title, "Doctor of Medicine," or its abbreviation, "M.D.," and that he was not entitled to engage in the general practice of medicine and surgery. In the latter part of 1950, the state board of health filed certain charges against the petitioner, which, briefly stated, were using medicines of doubtful value, imposing excessive charges, making unjustified promises of cure and deceiving patients about their physical conditions, following unorthodox diagnostic procedures, employing scare tactics, and failing to provide for adequate relief of pain. Among other grounds for reversal, the petitioner contended that the evidence did not sustain the board's action.

The Court of Appeals said that uncontroverted testimony was developed to the effect that the petitioner had paid for a listing in the Louisville telephone directory as "Doctor of Medicine," although he did not have this professional status, and had in 1944 and several times thereafter been warned by the board to have the listing removed. This warning he ignored until this proceeding was begun. He also gave the "Koch shots" for cancer treatments, with knowledge that after investigation the American Medical Association had branded the use of such a substance valueless therapeutically. It was brought out that the petitioner charged $100 to $150 for each "Koch shot," while the cost of each shot to him was only $25. He gave conflicting testimony as to what the services for each charge involved. It was stated that the petitioner refused to relieve pain on two occasions and employed methods that terrorized on another occasion. These last two assertions were denied by him. There was proof that the petitioner claimed in several instances that "Koch shots" would cure cancer. He refuted this testimony in part. The testimony introduced before the board concerned patients whose conditions were diagnosed and treated by the petitioner as cases of cancer. It is common knowledge that medical science has as yet discovered no drug that will cure this disease in its advanced stage. Despite this fact, it will be recalled, continued the court, that the petitioner gave assurance, according to the testimony of Everett Rucker, that he could heal the latter's wife, who was suffering from cancer in an aggravated form. He gave her three "Koch shots" at a cost of $100 per shot. Her illness was so advanced it should have been apparent to petitioner that he could do nothing to save her life. It has been held that the acceptance of money upon the promise or representation of being able to cure a disease regarded by the concensus of medical opinion as incurable constitutes such unprofessional and dishonorable conduct as would warrant a license revocation. Considering the evidence that was not controverted and that the board could have believed, said the Court of Appeals, it could only with difficulty be held that the board's order was not supported by any substantial evidence. Nor can it be said its decision was not an honest and impartial one.

The petitioner also contended that he had not been accorded a fair and impartial trial. One of his arguments was that, over a year after the hearing, the counsel for the board filed with it a copy of an opinion and order of the Federal Trade Commission in the matter of Koch Laboratories, Inc., and others, as respondents. Briefly stated, this opinion held that the "Koch shots" in their various compounds have no therapeutic value in the treatment of cancer or tuberculosis nor any beneficial effects as healing drugs and, furthermore, that they have adverse effects on some persons when employed as a curative agent; and the order directed the respondents to cease disseminating these preparations by any means through the channels of commerce. Our answer to that, said the Court of Appeals, is that the opinion was a finding of law and not one of fact; hence the board could take judicial notice of it. Especially is this true since the Federal Trade Commission opinion was later affirmed by the United States Court of Appeals for the Sixth Circuit.

The petitioner's other grounds for reversal were also overruled, and the judgment of the trial court upholding the board's revocation order was accordingly affirmed. *Bandeen v. Howard, 299 S.W. (2d) 249 (Ky., 1957).*

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Hepatic Function in Tuberculous Diabetics Treated with Carbutamide. G. L. Luisetti, G. Abbate and A. Corsitto. Minerva med. **48**:538-543 (Feb. 17) 1957 (In Italian) [Turin, Italy].

Carbutamide was given by mouth to 15 diabetic patients with pulmonary tuberculosis as a substitute for insulin. The tuberculosis was severe in some patients and very severe in others. Impaired liver function was present in almost all patients. The diabetes was severe in only 1 patient, and carbutamide did not benefit this patient. The drug benefited the rest of the patients. Two patients were treated with carbutamide alone. Insulin was discontinued successfully as soon as carbutamide therapy was started in 7 patients, and their glucose metabolism became normal. Insulin was discontinued 2 or 3 weeks after treatment with carbutamide was started in 3 patients, and favorable results were obtained. Insulin had to be continued for 6 months in 2 patients. Two patients with very severe tuberculosis and severe diabetes already had marked functional disturbance of the liver. Treatment with carbutamide caused improvement of the metabolic syndrome, but the hepatic dysfunction became worse. The authors believe that patients with hepatic dysfunction should not take more than 2.5 Gm. of carbutamide per day. Treatment with this drug had no effect on the liver function of the remaining 13 patients.

Management of Shock with Corticotropin (ACTH) in Myocardial Infarction. V.-M. Anttonen and A. Rautakoski. Ann. med. int. Fenniae **45**:183-194 (No. 4) 1956 (In English) [Helsinki].

The authors present observations on 159 patients with myocardial infarction in whom the diagnosis was based on generally accepted clinical and laboratory criteria, and in 153 patients it could be confirmed by electrocardiographic changes. Six patients died soon after admission, and, therefore, electrocardiographic examinations could not be performed. All patients received anticoagulant therapy in the form of heparin, dicumarol, or marcumar. Ninety-five (60%) of the patients were admitted to the hospital within 24 hours of the attack. Clinical symptoms of shock were present in 79 patients (about 50%) at the time of admission to the hospital. Corticotropin was given to 86 patients, 60 of whom showed signs of shock, whereas such signs were present in only 19 of the 73 patients who served as controls.

Corticotropin was administered intramuscularly in daily doses of 10 to 80 units, depending on the severity of the symptoms. All but 10 of the 86 patients were given a preparation that had a prolonged effect. Seventeen of the 86 patients treated with corticotropin died, that is, 14 of the 60 who were in shock and 3 of the 26 who did not have clear symptoms of shock. There were 18 deaths among the 73 patients in the control series, that is, 11 of 19 patients who had signs of shock and 7 of 54 without signs of shock died. Treatment with corticotropin, however, did not save a single patient in profound shock (blood pressure, zero), but it seemed to be especially effective among those with moderately severe shock. It may also prove helpful in the prevention of shock. In the doses administered (10 to 80 units daily), corticotropin did not increase the signs of cardiac decompensation or the incidence of thromboembolic complications.

The Treatment of Hæmochromatosis with Particular Reference to the Removal of Iron from the Body by Repeated Venesection. P. M. McAllen, N. F. Coghill and M. Lubran. Quart. J. Med. **26**:251-276 (April) 1957 [Oxford, England].

Hemochromatosis is characterized by the deposition throughout the body of iron in the form of hemosiderin. The authors are concerned with the idiopathic form of hemochromatosis, not with exogenous or transfusion hemochromatosis, which results from multiple blood transfusions for chronic anemia. The heaviest concentrations of iron occur in the liver and pancreas. Next to these, the organs most severely affected are usually the thyroid, anterior pituitary, and heart. Fibrosis is associated with these iron deposits, invariably in the liver and frequently in the pancreas, thyroid, and heart. The main clinical effects of the disease are cirrhosis of the liver, diabetes mellitus, hypogonadism, and congestive cardiac failure. Asthenia and pigmentation of the skin are also common manifestations. Once symptoms have become severe, progressive deterioration commonly occurs. Death usually results within a few years from damage to the liver, pancreas, or heart, or it may result from intercurrent infection, such as pneumonia or tuberculosis. The authors present observations on 6 men, ranging in age from 46 to 58 years, whom they treated for hemochromatosis. The diagnosis was established in all by liver biopsy—in 4 by needle puncture and in 2 at laparotomy. The hematological state and the function of organs mainly affected (liver, pancreas, thyroid, and heart) were studied before treatment commenced. A diet containing 100 Gm. of protein and

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The place of publication of the periodicals appears in brackets preceding each abstract.

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about 7 mg. of iron was taken daily by all patients. No vitamin supplements were prescribed. Insulin was given for diabetes in 2 of the patients and thyroxine for the hypothyroidism in 1 patient. Congestive cardiac failure in 1 patient was treated by orthodox methods. Testosterone therapy was refused by the patients with hypogonadism. A phosphate mixture (potassium dihydrogen phosphate and disodium hydrogen phosphate) was given before meals, in view of the theoretical possibility that it could diminish iron absorption; and calcium lactate or gluconate was given between meals to combat any associated interference with calcium absorption, particularly since osteoporosis may occur in hemochromatosis and was already present in 2 patients.

Removal of 500 ml. of blood by venesection every week was planned for each patient. Direct venepuncture in the antecubital fossa or forearm was performed with a standard blood-taking set, local anesthesia being required by only 3 patients. The veins were used regularly for 2 to 4 years without difficulty. The blood was removed without reinfusion of separated plasma. Throughout the course of treatment, the patients carried on with their normal work and attended hospital for venesection during off-work periods. In 2 patients, the weekly venesection had to be reduced to 350 ml. because of tiredness in 1 patient and faintness in another. Otherwise large amounts of blood were removed without ill effect, and, eventually, a state of anemia was produced. By this time the excessive iron stores in the body were almost exhausted, as demonstrated by liver biopsy. Relief of symptoms was obtained in all patients, and an improvement in the functions of the liver, thyroid, and heart occurred in those in whom these organs were involved. Insulin requirements decreased in 1 of the 2 diabetic patients. After the iron stores in the body had been reduced, it was found that maintenance venesection of 1 to 2 liters per year was required in order to combat reaccumulation of iron. The authors believe that the prognosis in hemochromatosis is likely to be much improved by venesection and that by maintenance venesection the progress of the disease may be arrested.

Medical Management of Peptic Ulcer. C. A. Flood. Am. J. Gastroenterol. 27:457-470 (May) 1957 [New York].

In the long-term management of patients with gastric ulcer, the possible development of carcinoma makes continuous vigilance necessary. In a group of 101 patients with benign ulcer, followed for a period of 5 to 6 years, 5 patients developed gastric carcinoma from 3 to 19 years later. A series of 103 patients with benign and malignant antral disease, seen during the period 1947 to 1950, were recently resurveyed. Radiologic examinations had revealed evidence of a diseased antrum. After gastroscopy, 73 patients were considered to have benign disease of the antrum. Carcinoma that involved the antrum was found in 30 patients. Among the 29 patients in whom operation was performed, gastric resection was done in 23. Follow-up revealed that 7 of these patients survived 5 or more years and that 6 were alive at follow-up. The tumors were of either the superficial spreading or the fungating variety. An aggressive surgical approach is recommended, whenever there is continuing reasonable doubt as to the nature of the lesion.

Oral Maintenance Treatment of Pernicious Anæmia. J. F. Adams. Scottish M. J. 2:151-153 (April) 1957 [Glasgow].

Assessment of the value of oral treatment of pernicious anemia with commercial preparations of vitamin B_{12} and intrinsic factor seemed desirable, because of differences of opinion about the value of such substances in maintenance therapy. A trial of commercial vitamin B_{12}–intrinsic factor compound in 73 patients with Addisonian pernicious anemia over periods of 16 to 36 months is reported. On the basis of red blood cell counts and serum vitamin B_{12} levels, at a dosage level of 1 tablet per day (70 patients) and 2 tablets per day (3 patients), therapy was unsatisfactory in 35 patients, including the 2 patients on the larger dosage. It is concluded that such preparations are unsuitable for maintenance treatment of pernicious anemia.

Evaluation of the Medical (Conservative) Treatment for Peripheral Vascular Disorders: A Survey of 1000 Treated Cases Occurring in a Series of 2300 Consecutive Records of Patients with Circulatory Disturbances. D. W. Kramer, P. K. Perilstein and A. De Medeiros. Angiology 8:129-144 (April) 1957 [New York].

A survey of 2,300 case records, giving a total of 1000 treated patients with various peripheral vascular disorders, was studied, and the effects of therapy were evaluated. Pavex, mecholyl iontophoresis, intermittent venous compression, and the Sanders bed were used among the physical medicine procedures used during the last 25 years to improve the circulation. The vasodilating drugs had been developed to induce a more definite dilatation of the vessels, and the therapeutic application of anticoagulants had been recognized. Arteriosclerosis obliterans, diabetic atheromatosis, and arterial thrombosis were the conditions most commonly met among the arterial disorders. The incidence of gangrene in patients with thrombosis, excluding thromboangiitis obliterans and diabetes, was minimal. Thrombophlebitis was prevalent in patients with venous disorders; their number seems to be increasing. Embolectomy was performed in patients in whom embolic occlusion was detected early enough; the results were very satisfactory. Some of the patients underwent sympathectomy.

The results of treatment were good in 381 (54.9%) of the 1000 patients and moderate in 259 (37.4%); there were 53 (7.7%) failures. Good results were obtained in 254 patients with venous disorders (76.1%); 73 (21.8%) showed a moderate improvement, and 7 (2.1%) were failures. Some patients with common changes in the abdominal aorta were included in this series. Under treatment, the patients were able to continue their activities and lived for 5 to 10 years in comfort. Further advances in biochemistry and the study of hormones eventually may lead to progress in the treatment of thrombosis and be helpful in inducing a regression of this pathological condition.

Gastric Ulcer: Evaluation of Methods of Treatment. R. J. Bolt, W. S. Wilson and H. M. Pollard. Univ. Michigan M. Bull. 23:126-134 (April) 1957 [Ann Arbor].

A study was made at the University of Michigan Hospital for the purpose of evaluating the accuracy of diagnosis in cases of benign gastric ulcer, the results of surgical and medical treatment over a 5-to-10-year period, and the incidence of development of carcinoma in these cases over a similar period. The series included 227 cases of gastric ulcer, 189 benign and 38 malignant. The follow-up study included 150 of the 227 cases. It was found that, when all available procedures indicated a benign lesion, the diagnostic error was 2.8%. When x-ray and gastroscopic examinations gave conflicting evidence, about 25% of the lesions proved to be malignant. When both procedures indicated malignancy, about 50% of such lesions actually were malignant. The follow-up study showed that surgical treatment gave better results in general than did medical treatment in the cases of benign gastric ulcer. Although 8 patients eventually died of carcinoma, in no case was the lesion associated with the gastric ulcer for which the patient had been treated.

The study suggests the following conclusions: 1. In the differential diagnosis of benign and malignant gastric ulcer, the diagnostic error can be kept below the probable surgical mortality rate if all diagnostic techniques are used and the patients are kept under observation. 2. When results of diagnostic tests conflict, laparotomy and subtotal resection are advisable. Operation is indicated also in all cases of ulcer of the greater curvature of the stomach and in any case in which the lesion continues to cause symptoms or fails to diminish in size after 4 to 6 weeks. 3. A histamine-fast anacidity may be considered diagnostic of malignant gastric ulcer. 4. Since malignant change rarely occurs in a benign gastric ulcer and since surgical treatment carries the risk of fatal operative complications, conservative medical treatment is indicated in many cases of benign gastric ulcer.

Six Years' Survival in Severe Systemic Lupus Erythematosus: An Analysis of 12 Cases. J. R. Haserick. A. M. A. Arch. Dermat. 75:706-714 (May) 1957 [Chicago].

The author reports on 12 patients with severe systemic lupus erythematosus who lived 6 or more years after acute episodes. Of the 12 patients, 11 received steroid therapy in 1 or more forms. In 5 patients, steroid therapy was gradually discontinued and its resumption was not necessary. Two patients did not require cortisone or corticotropin for 2 years; then they relapsed, and hormone treatment was resumed. The most striking therapeutic response was noted in 2 patients who were given combined treatment with steroids and nitrogen mustard, the latter drug in 2 courses. A severe leukopenia developed in 1 patient 10 days after the second course of nitrogen mustard. Associated with the drop in leukocytes and other manifestations of impending agranulocytosis, results of the L. E. test changed from positive to negative. It remained negative for 6 years, and the remission was complete except for a persistently high sedimentation rate. Osteoporosis was a serious complication attributed to prolonged steroid therapy in 1 patient who had 2 compression fractures. Symptomatic relief was obtained from administration of testosterone cyclopentylpropionate for several months. Antimalarial drugs, such as quinacrine hydrochloride and chloroquine phosphate, may reduce the amount of steroids required and may be effective agents against photosensitivity. Prednisone and prednisolone have been of unquestioned value. They may be used as substitutes for cortisone or hydrocortisone, but the effect of their prolonged use is yet to be evaluated.

The clinical remissions noted in these patients were stable enough to enable them to tolerate dental extractions, emergency major abdominal and chest operations, fracture reductions, pregnancies, and repeated exposures to the sun. Pregnancy, while not recommended because of the additional technical burdens, should be permitted to go to term. The L. E. tests, previously positive, became negative in all patients, though only temporarily in some; and the serum protein electrophoretic patterns became normal in some patients. These improvements do not necessarily indicate a permanent remission. Occasionally proteinuria and increased casts and erythrocytes in the urinary sediment may disappear during a prolonged remission. With steroid therapy, the instability of the disease can be controlled. Such treatment is indicated in systemic lupus erythematosus for as long as control of the disease is necessary and until a natural remission occurs. It is not indicated in mild forms of systemic lupus erythematosus. Stable remissions may occur, but the occurrence of true "cures" is doubtful in this disease.

Clinical Features of Polyarteritis Nodosa with Lung Involvement. G. A. Rose. Brit. J. Tuberc. 51:113-122 (April) 1957 [London].

Until about 15 years ago, periarteritis nodosa remained largely a pathological curiosity, but, at present, about half the diagnoses are made clinically, and the disease is no longer a rarity. Its early recognition has become important since the introduction of cortisone and corticotropin. This paper is concerned chiefly with the pulmonary manifestations of periarteritis nodosa, since these are unfamiliar and often lead to errors in diagnosis. This survey was based on a total of 111 proved cases of periarteritis nodosa. There was evidence of lung involvement in 33% of the patients. The respiratory illness in these patients generally preceded evidence of periarteritis in other organs and took the form of pneumonia, bronchitis, or asthma. Radiologically, the appearances of the lesions were varied, and no specific patterns could be recognized. A diagnosis of periarteritis nodosa should be considered whenever a patient with an atypical pulmonary disease has unexplained lesions in other organs, especially if there is also eosinophilia or asthma.

Pathological proof of the diagnosis should be obtained before starting cortisone treatment, for, if the latter is to be effective, it may require prolonged and heavy dosage. Deaths attributable to cortisone have occurred in patients treated on a mistaken clinical

diagnosis of periarteritis nodosa, when the patient required different therapy. Fortunately, it is possible in most cases to obtain proof of the diagnosis by biopsy. The highest proportion of success is achieved by biopsy of skin lesions. These, however, must be recent and nonulcerated; for, on the one hand, healed arterial lesions may be unrecognizable and, on the other, ulceration and secondary infection make it impossible to determine whether vascular changes are primary or secondary. In the absence of suitable skin lesions, "blind" muscle biopsy probably offers about a 50% chance of positive findings, equivocal findings being much less common than in skin biopsy. The most suitable sites are probably the pectoral or calf regions. The volume of muscle removed must be sufficient to contain several small arteries.

Early Diagnosis in Cancer Detection Clinics Yields 70% Cure Rate. C. B. Hess. Pennsylvania M. J. **60**:611-612 (May) 1957 [Harrisburg].

Of 108 persons with cancer found among 14,529 persons who had 38,023 examinations at the Philadelphia Cancer Detection Clinic, 30,912 of which were performed on women and 7,111 on men, 6-month checkups were carried out in 64, and checkups were at 12-month or longer intervals in the remaining 44. Of the 108 cases of cancer, 15 were in men and 93 in women. In all, cancer was discovered or suspected in the clinic and subsequently confirmed by positive biopsies. Most of the patients returned to their family physicians after discovery of the cancer and continued with them for periodic checkups. Of the 108 patients, the breast was the site of the cancer in 35, the colon and rectum in 18, the skin in 13, the fundus uteri in 13, the uterine cervix in 8, the thyroid in 4, ovary in 4, prostate in 3, lung in 1, gallbladder in 1, urinary bladder in 1, and stomach in 2; 3 patients had sarcoma, and 2 had leukemia. The 5-year survival rate was unusually high and was attributed to early diagnosis. The survival rate was 100% in patients with cancer of the uterine cervix, 87.5% in those with cancer of the skin, 66% in those with cancer of the fundus uteri, 75% in those with cancer of the rectum and colon, and 60% in those with cancer of the breast. The general survival rate was 70% in the patients with cancer of the breast, skin, cervix, fundus, colon, and prostate. There were no 5-year survivals in patients with cancer of the lung or ovary or in those with sarcoma or leukemia.

Partial Addison's Disease. J. Pedersen and E. Søndergaard. Ugesk. læger **119**:347-351 (March 21) 1957 (In Danish) [Copenhagen].

Comparatively mild cases of primary insufficiency of the adrenal cortex, characterized by a 17-ketosteroid content in the blood or urine that lies within the normal range but does not increase after stimulation with corticotropin, as in normal persons, have been designated as partial adrenocortical hypofunction. In a man, aged 57, with nervousness, dyspepsia, gout, slight pigmentation, and slightly reduced 17-ketosteroid excretion, but with a nonpathological corticoid excretion, normal electrolytes, and normal blood pressure, diagnosis of partial adrenocortical hypofunction was made. The excretion of the total amount and fractions of the neutral 17-ketosteroids did not increase on powerful stimulation with corticotropin. On increasing cortisone administration the pathological Kepler-Robinson test became normal, likewise the pigmentation and the other symptoms disappeared. The diagnosis of partial adrenocortical hypofunction is easily overlooked. It can at present best be made by the application of steroid analysis before and after stimulation with corticotropin. With the aid of the corticotropin test, the distinction between primary and secondary insufficiency of the adrenal cortex can as a rule be made, and adrenal insufficiency can be diagnosed even though the amount of steroid does not fall outside of the normal range.

SURGERY

Duodenal Tumors. F. Deucher. Arch. klin. Chir. **285**: 134-159 (No. 2) 1957 (In German) [Berlin].

The authors describe 11 cases of tumors of the duodenum, 5 of which were benign and occurred in men between the ages of 31 and 76, and 6 of which were malignant and occurred in a 57-year-old woman and in 5 men between the ages of 45 and 68 years. Three patients with benign tumor, 1 with neurinoma, and 2 with adenomas of Brunner's glands of the duodenum were operated on and have recovered. The 2 other patients with benign tumor, a 76-year-old man with 2 sharply outlined polyps the size of a hazel nut in the duodenal bulb and a 31-year-old man with duodenal polyposis, were not operated on. Surgical treatment was not considered in the first patient because of his advanced age. The other patient, who had had heartburn and eructations for about 7 years and a mild hypochromic anemia suggesting the occasional occurrence of occult hemorrhages, was advised to submit to regular control examinations. Three of the 6 patients with malignant tumor were operated on. Of the 3, one who had a suprapapillary stenosing adenocarcinoma in the descending portion of the duodenum removed by duodenopancreatectomy was well and his work capacity was completly restored 4 years after the operation. The 2 others had peripapillary adenocarcinomas that likewise were removed by duodenopancreatectomy; both patients were well and free of recurrence 1½ and 2½ years, respectively, after the operation. The 3 remaining patients had infrapapillary carcinomas that were no longer operable when the diagnosis was made.

Patients with suprapapillary tumors vomit old food particles but no bile, making differential clinical diagnosis from pyloric stenosis difficult, but the roentgenograms show widening of the duodenal bulb and also dilatation of the pylorus in addition to gastric extasia. Retention of bile is the predominant symptom of peripapillary carcinoma, and many of the patients may have the classic symptoms of obstructive jaundice, making a correct clinical diagnosis difficult. The diagnosis of infrapapillary tumors is probably the most

difficult one to make, because the inferior horizontal portion of the stomach is not visible in the roentgenogram. The fact that the vomited matter contains large amounts of bile and that the stools may have become lighter despite the absence of jaundice may aid in the diagnosis, but the right time for a radical operation may have been missed in most patients, since the superior mesenteric artery had been surrounded already by the tumor. Palliative surgical treatment in the 3 patients with this type of tumor consisted of the performance of gastroenterostomy.

Considerable diagnostic difficulties may arise from so-called pseudotumors. In 1 of the patients with infrapapillary tumor of the duodenum, the correct diagnosis was made only during operation because the stenosing duodenal carcinoma was masked by a perforated ulcer in the bulb, which was associated with an encysted abscess. Similar radiologic appearances that may be responsible for an erroneous diagnosis may be observed in patients with an annular pancreas and with a mobile duodenum. Conditions, such as transpyloric prolapse of the gastric mucosa, prolapse of a pedunculated gastric polyp into the duodenal bulb, extramural processes, periduodenitis, prolapse of Vater's papilla into the duodenal wall, and perforation of carcinoma of the head of the pancreas into the duodenal wall, may cause erroneous diagnosis.

Cholelithiasis Mirrored by Statistics. U. J. Wassner. Arch. klin. Chir. **285**:160-182 (No. 2) 1957 (In German) [Berlin].

Of 842 patients with cholelithiasis operated on between 1948 and 1955, 136 were men and 706 were women; women thus predominated in a ratio of 5 to 1. The average age at the time of the operation was 47.69 years, and the average age of the men at the time of the operation was 7 years above that of the women. About 32% of the patients, however, were operated on between 16 and 39 years of age, and only 24% were operated on between 40 and 50 years of age. There is no typical age at which patients with cholelithiasis are subjected to surgical treatment. The age at which the operation is performed ranges almost evenly from the 30th to the 60th year of life. The typical age at the onset of cholelithiasis is between the 20th and 30th year of life.

Three hundred ninety-one patients stated that they had a severe general infection several years before the appearance of the first symptoms of cholelithiasis; 12.7% of the patients had rheumatic febrile diseases, 11.9% diphtheria with pareses, 11.9% renal disease with high fever, 10% pleurisy, 7.5% typhoid fever, 6% pneumonia with pulmonary abscess, 5.6% otitis, 5.3% tonsillitis, and 5% primary tuberculous infection. It, therefore, seems very likely that a severe general infection may be the cause of the occurrence of biliary calculi. Of 521 patients who were followed up after the operation, 319 were free of complaints and 202 still had complaints, a ratio of 61% to 39%. The prognosis is more favorable the earlier in life and the earlier after the onset of the first complaints the operation is performed. The prognosis becomes less favorable, not only with advancing age but particularly with every year that elapses after the onset of the first symptoms. Patients over 45 years of age have only a slight chance to become free of their complaints.

The operative death rate was below 1% in patients under 35 years of age; it showed a pronounced increase in patients between the ages of 55 and 65 years, and nearly every second patient aged over 70 years died. The average operative mortality due to cholelithiasis is 6.8%, but most of the deaths occur in patients over 65 years of age. The operative mortality among patients of middle age who are operated on is 4%. A relationship between cholelithiasis and pregnancy cannot be established with the aid of statistics and the same applies to a relationship between cholelithiasis and carcinogenicity. The number of patients with postoperative complaints can be reduced only if one operates on a patient while he is still young and as soon as possible after the onset of the first symptoms. If this postulate is fulfilled, a reduced death rate after surgical treatment of cholelithiasis certainly can be expected.

Complaints After Cholecystectomy. E. Kaiser. Schweiz. med. Wchnschr. **87**:251-255 (March 16) 1957 (In German) [Basel, Switzerland].

The author cites evidence indicating that associated disorders, such as duodenal diverticula, duodenal and ventricular ulcers, pancreatitis, diaphragmatic hernia, coronary sclerosis, bronchiectasis, and diabetes, are responsible for complaints after cholecystectomy in up to 25% of the patients. He describes measures taken either to rule these out or to detect and treat them and then reviews follow-up studies on the first 100 of the 450 patients with disturbances of the biliary passages in whom these measures were carefully adhered to. The group included 83 women and 17 men, and they were operated on between 18 and 30 months previously. Seventy-four feel well and are satisfied with the results of the operation, but 17 of these 74 adhere to a somewhat restricted diet, whereas the remaining 57 can eat anything. Twenty-six patients still feel sick, and all of these are upset by fats. Fourteen of these 26 have complaints not directly connected with the disorder for which the operation was performed. In 11 of the remaining 12 who have residuals of the disease for which they were surgically treated, the operation disclosed serious pathological changes in the liver. In 5 of them the bacteriological tests on the A bile were positive, and in 1 patient a carcinoma of the pancreas had been overlooked. During the operation, serious pathological changes were observed in the liver in 32 patients, and the bacteriological test on the A bile was positive in 12. In 13, these 2 conditions were combined.

The organisms found were chiefly Escherichia coli, enterococci, streptococci, and micrococci (staphylococci), and the most important hepatic lesions were cholangiitis, hepatitis, and various forms of cirrhosis. The fact that only 12 patients had residual complaints that were connected with the biliary passages indicates that a large percentage of even the severe infections

and pathological changes, such as duodenal papillitides, choledocholithiasis, and cholangiitis, are being cured. Owing to the fact that now cholangiography and cholangiomanometry is often being done during the operation, calculi in the cystic duct or in the choledochus are now rarely overlooked, and, for this reason, postoperative results should be better now than they were formerly. Since these examinations are being carried out during operations, the causes of the postcholcystectomy symptoms have changed. No longer are overlooked calculi the chief problem but rather the changes in the liver, particularly cholangiitis, interstitial hepatitis, and the various forms of cirrhosis. Nowadays the fault lies less often with the surgeon and more often with the patient, who did not consent to an operation early enough. The author does not imply, however, that every patient with gallstones should be operated on. Cardiac decompensation, a recent infarct, and a decompensated renal disorder are still absolute contraindications, and advanced age, arteriosclerotic dementia, and extreme obesity are still relative contraindications, provided the acuteness of the process does not make the operation unavoidable. Early operation, before the development of complications, will improve the results of gallbladder operations.

Course and Management of Hirschsprung's Disease. G. G. Wyllie. Lancet 1:847-850 (April 27) 1957 [London].

This is the first of 2 reports on 152 patients with congenital megacolon (Hirschsprung's disease). There was great variation in the severity of symptoms. One child might not be seriously disturbed for some years, whereas another might have acute obstruction and be severely ill in the first days of life. Yet the 2 might have apparently identical lesions. The length of the aganglionic segment was an important, though not the only, factor. The diagnosis could be presumed on clinical evidence, but confirmation was sought by roentgenologic examination. The opaque enema was a useful diagnostic aid in patients of any age, even in babies a few days old. Interpretation of the findings in young babies might be difficult, however, for at this age the contrast between the unexpanded segment and the colon above it might be slight. Rectal biopsy proved useful. In the present series specimens were obtained by submucous resection, and the diagnosis was based on the state of the submucous parasympathetic plexus. The author discusses the differential diagnosis between congenital megacolon and other forms of chronic obstruction associated with enlargement of the colon. The mortality in patients with untreated congenital megacolon was high. Formerly, many infants died of obstructive crises, and few survived to adult life.

The authors attempted to develop a standard procedure for each aspect of congenital megacolon until Swenson's operation (excision of the aganglionic intestine) could be performed. In the neonatal period, if the signs were mild, a finger or tube passed into the rectum usually established the flow of meconium. This procedure was repeated if meconium and, later, feces and gas tended to be retained. Many infants did not need any early treatment other than this. If rectal examination failed to produce a significant amount of meconium and gas, colonic lavage was carried out. This had to be done with great care, for the wall of the intestine might be thin, and perforation may occur either by the tube or from increased tension within the lumen.

If the diagnosis was not made until laparotomy, treatment depended on the length of the aganglionic segment. If the cone was at the rectosigmoid junction or in the lower part of the sigmoid colon, a rectal tube was passed and guided into the dilated intestine. Deflation could be achieved in this way and a colostomy avoided, as subsequent colonic lavage could be expected to keep the colon empty. An enterostomy was necessary if the abnormal segment extended further along the intestine, but most infants did not need operation in the immediate postnatal period. Gaseous abdominal distension might be controlled by the passage of a flatus tube or a finger regularly before feeding. Acute obstructive episodes usually could be overcome by colonic lavage, but an emergency colostomy was needed occasionally. The infant could be helped to thrive so well that excision of the aganglionic intestine (Swenson's operation) could be carried out as early as the age of 6 weeks. Some children with congenital megacolon go through childhood with no more inconvenience than that of a slightly enlarged abdomen and moderate constipation that responds to aperients, but even these children may suffer from physical and sexual retardation, and their condition would be improved by Swenson's operation, which the author regards as the treatment of choice in practically all cases.

Treatment of Hirschsprung's Disease by Swenson's Operation. G. G. Wyllie. Lancet 1:850-855 (April 27) 1957 [London].

In this paper the author reports his experiences with excision of the aganglionic segment of the intestine (Swenson's operation) in 152 children, 128 boys and 24 girls. The early cases were mostly in older children who had survived the disease for several years, but it was quickly found that younger children and infants withstood the operation well, and much malnutrition and chronic ill health was thereby avoided. During the past few years, the diagnosis has been made increasingly often early in life, and early operation has become the rule. The youngest age at operation was 5 weeks. Initially transverse colostomy was performed routinely in 3 stages—colostomy, excision of aganglionic intestine, and closure of the colostomy. Since 1952, single-stage operations have been performed, and this has become the standard practice. The following circumstances are now regarded as indications for preliminary colostomy: (1) acute obstructive episodes in the neonatal period or infancy that cannot be relieved by colonic lavage; (2) an unusually long narrow aganglionic segment, revealed at laparotomy, causing an obstruction that cannot be relieved by guiding a rectal tube into the dilated intestine; (3) infants who do not thrive despite regular colonic lavage; and (4) older children with

advanced disease and gross colonic dilatation and hypertrophy. The transverse colon was usually the site of the colostomy. The essential measure in preparation for the operation is to empty the large intestine. Daily colonic lavage has proved the most satisfactory method. In some long-standing cases many weeks of treatment may be necessary. Enemas are generally ineffective and are potentially dangerous. Immediately before operation a bacteriostatic or antibiotic agent is given orally. Both succinylsulfathiazole for 5 days and streptomycin or oxytetracycline for 2 days have proved effective.

The Swenson technique as modified by Dennis Browne was used in most cases. Single-stage operations were performed on 66 children, while 86 had preliminary colostomies. The operation consisted in mobilization of the aganglionic intestine down to the anal canal, the dissection below the peritoneal floor being made on the rectal wall. In selecting the site of proximal section, the most important factor is that it should be in normally ganglionic intestine. Children withstand the operation well. In 35 of the 152 patients some complication occurred, and, of these children, 9 died. Complications were shock, ischemic necrosis of the distal colon, pelvic infection, disruption of the wound, intestinal obstruction, anastomotic stricture, urinary retention, and functional colonic retention. Children who are not yet 3 years old and who were not expected to be fully continent and children operated on during the 3 months prior to writing were excluded from the assessment of the functional results. This left 102, whose ages at the time of writing ranged from 3 to 22 years. A recent survey showed that 55 were normal in every way. The remainder still had some deficiency, but in most this was slight. Sixty-one of those over 3 years old had achieved full continence. Control was relatively good in 28 of the remaining 41 patients. In many patients constipation was an important cause of incontinence, and improvement usually followed correction of constipation. Intestinal training was another important factor after operation. Many of these children had never experienced the normal sensations associated with defecation. They failed to realize, or realized too late, the need for defecation.

Sympathectomies in Peripheral Vascular Diseases: Follow-up Studies to Twenty Years. R. J. Popkin. Angiology **8**:156-160 (April) 1957 [New York].

One hundred and eight consecutive sympathectomies were performed on patients with various peripheral vascular disorders from 1946 to 1955. The largest series included 60 patients with arteriosclerosis obliterans; 29 had thrombosis obliterans, and 19 had Raynaud's syndrome, primary Raynaud's disease, and scleroderma. The ratio of males to females was 3:1 for the group with arterial occlusion, and the age of the patients was from 43 to 76 years at the time of sympathectomy. Females exceeded the males 4:1 in the vasospastic group, their ages varied from 22 to 49. The arteriosclerotic patients underwent lumbar sympathectomy, in a few cases bilateral sympathectomy was performed. Most of the patients with thromboangiitis obliterans had cervical and lumbar sympathectomy, many of all 4 extremities. Cervical sympathectomy was performed in the patients of the other groups. All patients were observed and followed for a long period. The surgeons performed the operations, with varying indications, contraindications, and techniques. Patients with arteriosclerosis obliterans and thromboangiitis obliterans obtained satisfactory results only when the predominant symptom was vasospasm and when the patient was a good surgical risk. Increased warmth and healing of superficial ulcerations resulted in 50% of these patients. Intermittent claudication was not benefited by the operation; pains did not subside and lower level amputations for gangrene was not made possible. No benefit was obtained by sympathectomy in patients with scleroderma. Only 1 patient with primary Raynaud's disease had good results. Sympathectomy of the upper extremities were of value only for injury or causalgia. Patients with thromboangiitis obliterans who continued to smoke failed to obtain good results. Factors that should be taken into consideration in evaluating patients for sympathectomy are those of climate, terrain, and local customs of transportation. The emotional and physical condition of a patient should not be underestimated.

On the Changes in Plasma 17-Hydroxycorticosteroid Levels During Surgical Procedures. S. J. Viikari and B. H. Thomasson. Acta endocrinol. **24**:361-369 (April) 1957 (In English) [Copenhagen].

The 17-hydroxycorticosteroid level was estimated by means of methylene chloride extraction before, during, and after operation, in 11 patients subjected to thoracic operations and in 4 subjected to cholecystectomy. Eight of the 11 patients subjected to thoracic operations had pumonary tuberculosis, and 3 had pulmonary cancer. All 11 patients were given 25 mg. of chlorpromazine hydrochloride, 12 to 16 mg. of morphine, and 0.3 to 0.5 mg. of scopolamine before operation. Anesthesia was induced with 0.5 to 1.5 Gm. of thiopentol sodium, 100 to 150 mg. of meperidine, and suitable doses of muscular relaxants, usually 50 to 100 mg. of succinylcholine chloride and 50 mg. of Laudolissin. The patients were intubated and were given oxygen and nitrous oxide. A carbon dioxide absorber was used. Fifteen to 30 minutes elapsed between the beginning of the induction of anesthesia and the operation. The operation lasted from 75 to 135 minutes. No serious surgical or anesthetic complications occurred. The 4 patients subjected to cholecystectomy received morphine and scopolamine. Anesthesia was induced with ethyl chloride and continued with ether. Twenty to 25 minutes elapsed between the induction of anesthesia and the beginning of the operation, which lasted for from 35 to 60 minutes. The ether anesthesia used in the cholecystectomies caused a marked rise in the plasma levels of 17-hydroxycorticosteroids, while the thiopental-meperidine-nitrous oxide anesthesia used for the thoracic operations caused a decrease of these levels. The adrenocortical response to the operation was uniform in the different patients in spite of their variation in duration and severity. This is considered to be an indication that cholecystectomy and the thoracic operations involve a maximal or at least submaximal stimulation of the

adrenal cortex. One to 2 hours after the operations, the plasma levels were still increasing and were greatly above normal.

The Value of Phalangization in a Patient Who Had Lost All the Fingers of Both Hands. F. Fusi. Minerva ortop. 8:65-71 (March) 1957 (In Italian) [Turin, Italy].

The author reports on the case of a 54-year-old man with dry gangrene due to bilateral third degree freezing of the limbs. The patient was exposed to subzero temperatures after an accident in the Alps. The legs and the fingers of both hands had to be amputated. The skin of both hands was repaired with grafts. The 2nd and 4th metacarpal bones of the left hand were disarticulated. Phalangization of the 1st, 3rd, and 5th metacarpal bones was obtained by means of Z-shaped incisions. The first intermetacarpal space of the right hand was deepened. Altogether the patient was subjected to 10 operations in 8 months. He is satisfied with the appearance of his metacarpal hands. The result of the bilateral phalangization of the first metacarpal bones was excellent; the neophalanx obtained from the 5th metacarpal bone proved to be of little use. After appropriate training he became proficient in taking care of his most elementary needs.

Systemic Osteopoikilosis Due to Hydrofluorosis: Report of 1 Case. G. Nalbone and F. Parlato. Folia med. 40:81-99 (Feb.) 1957 (In Italian) [Naples].

Endemic hydrofluorosis is characterized by lesions of the teeth, osteosclerotic changes in the skeleton, disturbances of the digestive apparatus, and anemia. Hydrofluorosis is present in certain areas of the United States, Canada, Argentina, India, Africa, Italy, Switzerland, Spain, Scotland, Holland, Portugal, and Ireland. The authors describe the case of a 49-year-old farmer with hydrofluorosis. He was born and lived all his life in a fluoric zone in Sicily. The roentgenologic examination showed a massive and systemic eburnation of the whole skeleton with periostosis and endostosis, extended ossification of the fibrocartilaginous system with calcification of the vessel wells, and signs of gastroduodenitis.

GYNECOLOGY & OBSTETRICS

Hypotensive Drugs in Pregnancy Toxemia. W. B. Cherny, F. B. Carter, W. L. Thomas and C. H. Peete Jr. Obst. & Gynec. 9:505-511 (May) 1957 [New York].

Seventy-four pregnant women, 29 with pure preeclampsia, 39 with toxemia superimposed on a preexisting hypertensive state, and 6 with eclampsia, were given combined treatment with hydralazine (apresoline) hydrochloride and cryptenamine (Unitensen) acetates. The 2 drugs were given alternately, hydralazine in doses of 10 or 15 mg. and cryptenamine in doses of 0.2 to 0.4 cc. by hypodermic injection at hour or 2-hour intervals. In all 29 patients with preeclampsia the blood pressure was lowered, and 16 of them were subsequently discharged undelivered but free of clinical features of toxemia; 9 patients were within 3 weeks of term, and labor was induced after satisfactory control was established. The remaining 4 patients were therapeutic failures. In only 3 of the 6 patients with eclampsia was it possible to lower the blood pressure significantly before delivery. The poorest results were observed in the 39 patients with toxemia superimposed on preexisting hypertension. The average change in antipartum blood pressure was less in this group than in those with preeclampsia. The only cesarean section in the 74 patients was done in a patient who continued to get worse and in whom repeated attempts to induce labor were unsuccessful. Of 75 infants who were delivered, 64 were living and 11 stillborn, giving an over-all fetal salvage rate of 85.3%. Four of the 11 stillborn infants had died in utero before the institution of therapy; the corrected fetal death rate was 9.3%.

Since the causation and pathogenesis of toxemia of pregnancy remain unknown, the treatment must be confined to attempted correction of demonstrable abnormalities. Although reducing blood pressure and lowering peripheral resistance constitute but one phase in the over-all treatment of this disorder, there can be very little doubt that this is the most important aspect. Magnesium sulfate still remains the safest of the hypotensive agents. Derivatives of Rauwolfia serpentina have been unpredictable in the authors' hands, often inducing severe, prolonged hypotension and sometimes shock-like states. Most of the satisfactory results have been obtained with magnesium sulfate and mixtures of hydralazine and cryptenamine.

Postpartum Mental Illness: A Controlled Study. M. Foundeur, C. Fixsen, W. A. Triebel and others. A. M. A. Arch. Neurol. & Psychiat. 77:503-512 (May) 1957 [Chicago].

Postpartum mental illness includes any mental illness in a woman in which childbirth was a major precipitating factor. The group studied, identified as the experimental group, consisted of 100 women who were hospitalized for a mental illness that was judged to be precipitated by childbirth (mental illness precipitated by an abortion or by adoption being excluded). The control group consisted of 100 women who were admitted to the same hospital and matched for age and for year of admission but in whom childbirth was not a precipitating factor of the mental disturbance. There was no significant difference between the experimental and the control group as regards psychoneurosis, dementia praecox, or manic-depressive psychoses. The postpartum group did not include as many alcoholic and narcotic addicts, nor as many psychopaths as the control group. The concluding summary stresses the following points: 1. Postpartum mental illness is not a disease entity. 2. No one religious group showed a stronger predilection for such an illness than did any other group. 3. Almost one-half of these illnesses were in reaction to the birth of a second or a later child. 4. The postpartum patient was like any other female patient of the same age in respect to previous mental instability. 5. With regard to schizophrenia, postpartum patients had the same prognosis as did other schizophrenics. 6. About 75% of the postpartum patients were found to be at a reasonable level of recovery 4 years after their hos-

pitalization. 7. The chance of a subsequent mental illness following another pregnancy was only 1 in 7. 8. The condition in the postpartum patient had a favorable prognosis.

Action of Reserpine on Contraction of Uterus and Dilatation of the Cervix: Preliminary Report. D. F. Klauer. Prensa méd. argent. **43**:3702-3706 (Dec. 14) 1956 (In Spanish) [Buenos Aires].

Dilatation of the cervix is the longest period of labor. The author found that reserpine, used when the cervix starts to dilate, favors dilatation. The drug is injected intramuscularly in doses of 2 mg. When more than 1 injection is necessary, the interval is 2 hours. The drug acts as a tranquilizer for the mother, stimulates strong uterine contractions and dilatation of the cervix, and greatly shortens labor. In the 26 cases reported by the author, in which the drug was used, all the fetuses were born with eupneia. In only 1 case was there fetal suffering, and this was due to an abnormality of the umbilical cord. In 1 case the drug was used to induce delivery of a macerated fetus. The placenta was delivered normally in all cases within 5 to 15 minutes after delivery of the infant. The involution of the uterus was normal. The drug is harmless for the mother and for the fetus. It does not alter normal blood pressure.

Preoperative Cortisone for Vaginal Fistulas. C. G. Collins and F. B. Jones. Obst. & Gynec. **9**:533-537 (May) 1957 [New York].

Of 31 women with fistulas involving the vagina, 11 were treated preoperatively with cortisone. The patients were placed on a nonresidue diet and 100 mg. of cortisone was administered 3 times daily, with a total dose of 3 Gm. being given in 10 days. Because of the anti-inflammatory properties of cortisone and the risk of spread of infection, its administration was "covered" by the simultaneous administration of penicillin and a broad-spectrum antibiotic. The remaining 20 patients not previously treated with cortisone served as controls. Ten of the 11 patients, 8 with vesicovaginal fistulas and 1 each with a rectovaginal and a rectocervicovaginal fistula were cured; 1 with a vesicovaginal fistula was a therapeutic failure. Eighteen of the 20 control patients were cured, and 2 were therapeutic failures. The average time between discovery of the fistula and surgical repair in the 11 patients treated with cortisone was 4 weeks. The average time between discovery of fistula and surgical correction in 18 of the 20 patients was 94 weeks.

For decades the basic principle in the treatment of vesicovaginal and rectovaginal fistulas was to wait 5 to 6 months before any attempt was made to correct the fistula by surgery. This period of time was necessary, since early repair was associated with a very high rate of failure. Failure was due to the fact that the surrounding tissues in these fistulas were hard, indurated, thickened, and infected, causing difficulty in dissection, improper identification of tissues, and interference with wound healing. An average difference of 90 weeks in the time from occurrence of the fistula to successful closure was noted between the patients treated before early repair with cortisone and the control patients. This degree of success attained by the use of cortisone preoperatively and early operation warrants continued application of this procedure.

PEDIATRICS

Treatment of Infantile Eczema with Corticotropin and Cortisone. H. Klingenfuss. Ann. paediat. **188**:226-246 (April) 1957 (In German) [Basel, Switzerland].

In the first part of this paper the author reviews the literature on the use of cortisone and corticotropin in the treatment of infants with eczema, emphasizing that this treatment was first described by American authors in 1951. The second part of the report is concerned with the author's own experiences. He used cortisone or cortisone ointment in 3 infants with dermatitis seborrheica; in 23 children, ranging in age from 3 months to 3 years, with eczema infantum, and in 4 young children with neurodermatitis. Two children with Kaposi's varicelliform eruption are also mentioned, but in these 2 cortisone was ineffective. The favorable results obtained in the 30 children with dermatitis seborrheica, eczema infantum, and neurodermatitis confirmed earlier reports. The daily dose was 20, 40, or 80 mg. of cortisone by mouth, depending on the severity of the lesions. The duration of the treatment ranged from 5 to 48 days, with an average of 14 days. Except for a slight increase in weight in a 6-month-old infant, there were no side-effects. The most important advantages of cortisone therapy are rapid lessening of itching, regression of edema and erythema, and formation of a dry and clean skin. The greatest disadvantage is the almost regular recurrence of the eczema after discontinuation of therapy.

The author makes the following recommendations on the use of adrenocortical hormone in infantile eczema: 1. For mild lesions, local application of a 1% or 2% hydrocortisone ointment preferably combined with an antibiotic ointment, for instance cortimycin, which contains hydrocortisone and neomycin. This treatment can be continued for several weeks because absorption is slight. 2. For severe lesions, cortisone is given internally in daily doses of 40 or 60 mg. or prednisone is given in daily doses of 20 to 30 mg. Because a masked infection may exist, an antibiotic, such as penicillin, aureomycin, or terramycin, should be prescribed as well. To avoid side-effects, treatment with cortisone should not be continued for longer than 3 to 4 weeks. The best results are achieved in infantile eczema when cortisone therapy is combined with the customary treatment employing diet, ointments, and baths.

Antistreptolysin Levels in Premature Infants. E. Arditi and N. Nigro. Minerva pediat. **9**:170-173 (Feb. 17) 1957 (In Italian) [Turin, Italy].

The authors studied the antistreptolysin levels in 72 premature infants, 30 minutes to 133 days old, weighing 480 to 3,600 Gm. The antistreptolysin level in normal adults varies between 150 and 200 antistreptolysin units. The average level found in the in-

fants was 53.25 units. Levels below 12 units were not considered. Two infants had a level of 166 units; 21 born during the 7th month of pregnancy had an average level of 32.95 units; and 20 born during the 8th month of pregnancy had an average level of 84.35 units. Four infants born before the 7th month of pregnancy had very low levels, 2 under 12 units and 2 of just 12 units. The amount of antistreptolysin present in the body of 11 babies was measured every 15 days for 2 months, and it was found that it diminished especially after the 30th day of life. After 2 months, 5 babies of this group had levels below 12 units. The authors conclude that antistreptolysin is present but at very low levels in premature infants, that the level of antistreptolysin is related directly to the length of the pregnancy, and that the level diminishes progressively in the first period of extrauterine life.

An Examination of Factors Involved in the Transfer of Pyrimethamine in Human Milk. D. F. Clyde. East African M. J. 34:81-85 (March) 1957 [Nairobi, Kenya].

It has been found that pyrimethamine (Daraprim) is excreted in human milk and, thus, might eliminate parasitemia in breast-fed infants. The author evaluated indirect prophylaxis of infant malaria by treating mothers with pyrimethamine and determining (1) the extent to which women excrete the drug in their milk, (2) the amount of drug-containing milk taken up by the infants, and (3) the relationship of the amount of drug transferred to that required for the direct treatment of malaria. There was little difference in the amounts of pyrimethamine excreted in human milk after the treatment of lactating women with 50 or 75 mg. of the drug in a single dose. The quantity of drug appearing over a 2-day period in the milk is nearly twice that required for the cure of malaria by direct treatment of the baby, provided that the breast milk constitutes most of the child's diet.

In an urban and a rural area of Tanganyika, respectively, 90 and 96% of babies aged less than 3 months, 64 and 92% aged 4 to 6 months, and 39 and 71% aged 7 to 9 months were found to take breast milk in amounts sufficient to ensure that the accepted minimum curative dose of pyrimethamine was exceeded. Nevertheless there are reasons why the use of the drug indirectly by milk transfer is not indicated. First, resistance to pyrimethamine on the part of the most common parasite, Plasmodium falciparum, has now been demonstrated from localities in the Sudan, Kenya, and Tanganyika and is suspected for other species in Kenya and Ethiopia. Such resistance appears to have arisen in the course of prolonged drug administration. Second, under most circumstances, it would be no more difficult to arrange the attendance at clinic or community center of both mothers and babies for individual treatment as of mothers alone. Third, the larger doses required for indirect malaria prophylaxis in infants makes this method more costly than administration of the drug to mother and baby individually. In a mass drug scheme, involving individual treatment of persons of all ages, however, it may be reassuring to know that infants will receive additional pyrimethamine in their mothers' milk.

UROLOGY

New Treatment of Renal Tuberculosis. J. M. Gil-Vernet Vila and R. Gosálbez. Acta urol. belg. 25:61-74 (Jan.) 1957 (In French) [Brussels].

The authors recommend a new therapeutic method for renal tuberculosis that employs intermittent aspiration of the renal pelvis and direct local application of tuberculostatic drugs. Catheterization of the renal pelvis is accomplished with a plastic bougie with a caliber as large as the ureter will permit. This catheter is left in situ for from 15 to 20 days. While systemic administration of streptomycin, aminosalicylic acid, and, if necessary, hydrazides is continued, 20 cc. of a para-aminosalicylic acid solution is instilled through the indwelling catheter 3 or 4 times a day. It is of no importance if this quantity exceeds the capacity of the renal pelvis, because a pyelocanalicular reflux is believed to be beneficial. The solution is retained by closing the tube for from 10 to 15 minutes. Two illustrative case histories indicate that the indwelling-catheter treatment was given for 1 or 2 weeks out of each month.

The excellent results obtained with this treatment are ascribed to the following factors: (1) to the direct external drainage of the tuberculous foci, which avoids the development of secondary lesions; (2) to functional arrest of the renal excretory ducts; and (3) to direct local intracavitary tuberculostatic effect of the aminosalicylic acid solution. This action is superior to that obtained by systemic treatment due to the fact that the fibrosclerous covering that surrounds the tuberculous cavities prevents the antibiotic or tuberculostatic drugs to reach the tubercle bacilli in adequate concentrations. The method was easily carried out and completely harmless, and it effected the healing of cavities that would otherwise have required nephrectomy. Systemic administration of tuberculostatic drugs and dietetic and sanatorium treatment, however, should be combined with the described local treatment.

Obstructive Pathological Conditions in Relation to Male Fertility. J. Blackman. M. J. Australia 1:497-501 (April 13) 1957 [Sidney].

Of 110 men referred for investigation of infertility, 39 were found, after repeated semen analyses, to have azoospermia. Of the 39 patients, 21 had an obstruction of the excretory canal and 1 had retrograde ejaculation into the bladder. Of the 21 patients, 7 had epididymal occlusion without history of inflammation, 5 had chronic epididymitis, 4 had congenital absence of vas deferens, 1 had a cyst of epididymis and junctional failure of vasa efferentia, 1 had bilateral cysts of globus major, 1 had traumatic deficiency in vas deferens, and 2 had probable occlusion of ejaculatory ducts. Thus most of the patients with obstructive sterility had lesions of both epididymes. This is reasonable when one considers the length of the excretory canal (about 21 feet) and its small diameter.

In practice one must continue to be optimistic and encourage the patients in what must seem a hopeless predicament. Diagnosis can often be made clinically

and from the volume and quality of the ejaculate. Testicular biopsy is a valuable procedure when one is in doubt about spermatogenesis. Vasoepididymography with introduction of a 50% solution of iodopyracet into the excretory canal by the direct approach to the vas deferens at the neck of the scrotum may be performed simply and without morbidity and is of value in selected patients. It is not recommended as a routine procedure. Exploration of the scrotum with an attempt to reconstitute the seminal cause is recommended when possible. Vasovasal anastomosis usually gives good results, and vasoepididymostomy gives excellent results when there is a local block of motile spermatozoa in the head. In high obstructions to the head of the epididymis, the fertilizing power of the sperms is probably diminished, but if spermatozoa are detected, an attempt should be made to bring about the desired pregnancy by artificial insemination, if necessary. Due emphasis must be on preventing acquired obstructions to the genital tract by the avoidance of damage to the vas and vessels of the cord during operations for undescended testes, inguinal hernia, varicocele, or hydrocele. Even minor epididymal inflammation in young men should be vigorously treated, and bed rest should be instituted to facilitate rapid resolution.

Renal Liposarcoma. A. Ortiz, J. J. Guido, A. Corrieri and D. Hojman. Rev. argent. urol. **25**:132-136 (May-Aug.) 1956 (In Spanish) [Buenos Aires].

Renal liposarcoma is extremely rare. The tumor may appear at any age. It is more frequent in women than in men, and, as a rule, it is unilateral. Only 4 of the 8 cases previously reported in the literature were pure liposarcomas. The authors report 2 new cases of pure inter-renal liposarcoma in women 52 and 42 years old respectively. The tumor was located in the left kidney in 1 and in the right kidney in the other. The treatment consisted of nephrectomy. One of the patients was still alive and in good health 3 years after operation. The other patient died of uremia in the immediate postoperative period.

Sodium and Potassium Dehydrocholate as Diuretic Agents. A. Vogl and M. Kaizer. Angiology **8**:145-155 (April) 1957 [New York].

An attempt was made to establish more clearly the role of bile salts as diuretic agents. Sodium dehydrocholate had a potentiating effect on mercurial diuresis in 11 of 19 edematous patients; 6 had a fair and 2 had no response. Intravenous injections of 10 cc. of a 20% solution of sodium dehydrocholate (Decholin) were given slowly over a period of at least 5 minutes. They were well tolerated by all the patients. The toxicity of potassium dehydrocholate was studied in 10 patients with inoperable carcinoma or advanced senility, whose ages ranged from 65 to 85 years. Five to 10 cc. of 20% potassium dehydrocholate was injected slowly intravenously. No demonstrable side-effects and no significant electrocardiographic changes were observed. The results did not improve when potassium dehydrocholate was substituted for sodium dehydrocholate. This indicates that the sodium content of sodium dehydrocholate does not interfere with the diuretic effectiveness of the bile salt. The combination of sodium dehydrocholate and acetazolamide (Diamox) did not appear to have any appreciable effect on the diuresis.

OPHTHALMOLOGY

Diamox (Acetazolamide) in Cataract Surgery. L. P. Agarwal and S. R. K. Malik. Ophthalmologica **133**: 153-159 (March) 1957 (In English) [Basel, Switzerland].

It is generally believed that peripheral iridectomy prevents prolapse of the iris after cataract operation because it short-circuits the flow of aqueous humor. Since acetazolamide (Diamox) is known to diminish the formation of aqueous humor, the authors decided to use it in cataract extraction without performing peripheral iridectomy. They report observations on 300 patients who were admitted for cataract extraction to the hospital of the Medical College of Agra, India. Acetazolamide was given preoperatively to 100 patients; in another group of 100 patients, peripheral iridectomy was done; and the third group of 100 patients were used as controls. The group treated with acetazolamide received 1 delayed-action capsule (250 mg.) and 1 tablet (250 mg.) of acetazolamide 1 hour before the operation, and this treatment was repeated for 3 days. The incidence of iris prolapse in this group was reduced from 13 to 5%, which compares favorably with the iris prolapse rate of 4% in patients subjected to peripheral iridectomy. The incidence of flat chamber was negligible. Vitreous prolapse occurred in 6 of the patients who received acetazolamide, as compared with 10 in the group subjected to peripheral iridectomy and 11 in the control group, that is, it was reduced nearly half. The postoperative course was uneventful. It is suggested that the reduction in iris prolapse, vitreous prolapse, and flat chambers is due to the diminution of the flow of aqueous humor in the posterior chamber. Since, moreover, acetazolamide has a mild chemotherapeutic effect, the authors recommend its routine use in connection with operations for cataract.

Immediate and Late Complications and Late Deaths Occurring After Iridectomy with the Graefe Knife in Patients with Acute Glaucoma. F. Cuccagna. Ann. ottal. e clin. ocul. **83**:130-140 (March) 1957 (In Italian) [Genoa, Italy].

Sixty-two patients, 17 male and 45 female, were subjected to iridectomy. One patient was under 40 years of age, 12 were from 40 to 50 years old, 15 from 50 to 60, 21 from 60 to 70, 9 from 70 to 80, and 4 above 80. Complications were present in 17 patients at the time of discharge from the hospital. One had a cataract due to trauma to the lens capsule incurred during the operation. Three had hemorrhage into the anterior chamber, 3 endovitreal hemorrhage, and 1 retinal hemorrhage. Three had iritis. One had panophthalmitis and was treated before the advent of antibiotics. One had detachment of the choroid, and 4 had persistent endocular hypertension. Twenty-two patients were reexamined long after the operation. Cataract

was present in all 22 patients; the cataract was advanced and operable in 3 patients. Some patients had secondary hypertension with restricted vision.

A Three-Year Experience with Implantation of Polystan Sponge. F. Schwab. Wien. med. Wchnschr. **107:** 270-272 (April 6) 1957 (In German) [Vienna].

Polystan, an elastic polythene sponge, was used for the formation of the stump in 91 patients, in whom enucleation of the eye-ball was performed. Of these patients, 87 had normal postoperative healing and in 4 the polythene sponge had to be removed because of inflammation of the conjunctiva. The inflammation was due to the hardening of the sponge after it was cut out of a large sponge to obtain the required size. This inconvenience has been eliminated, since polythene sponges are now available in different sizes. Polythene sponge was well tolerated by the tissue, healing being uneventful even though the period of absolute rest in bed was reduced. Most of the patients were discharged 8 or 9 days after operation. The follow-up period was 1 to 3 years. The results obtained with the implantation of a polythene sponge in 87 of 91 patients were encouraging.

PATHOLOGY

The Malignity of the Cylindromas: Anatomoclinical Observations on 22 Patients with Cephalic Cylindromas. L. Pietrantoni and G. B. Leonardelli. Ann. otolaryng. **74:**15-31 (Jan.-Feb.) 1957 (In French) [Paris].

Certain histopathological and clinical observations on the malignity of the cylindromas are presented by the authors on the basis of the findings in 22 patients with genuine cylindromas observed and followed by them during the last 10 years and in 31 cylindroma-like tumors subjected to histological study. The methods of treatment used in these patients included simple enucleation of the tumor, followed by a 5-year cure in 1 patient; enucleation associated with roentgenotherapy in 7 patients, with one 7-year cure occurring; and radical surgical excision with removal of both the tumor and the organ concerned, e. g., the parotid and the submaxillary glands, the larynx, and the maxilla, in 18 patients followed by cures in 17 that have lasted 4, 5, 8, and 10 years or more, even when the tumor showed obvious histological findings of malignity. Local recurrences made a second radical operation necessary in 6 of these 17 patients, however. The postoperative supervision of the patients consisted of a series of checks, made first at monthly intervals and later at intervals of 3 months for periods ranging from 2 to 10 years. The patients so checked were also subjected to radiological examination of the skeleton and the respiratory apparatus every 6 months, because cylindromas have a tendency to produce latent osseous or pulmonary metastases.

The differential diagnosis of the cylindromas must be based on their histomorphologic appearance because the symptoms they produce are so much like those produced by "locally" malignant tumors (mixed tumors, invasive fibromas) and benign tumors that no distinction can be made between them. The uniformly slow course of the true cylindromas, their lack of invasiveness in the tissues in which they develop, the fact that they may be found in persons of any age, and their variability of localization also make the diagnosis difficult. The histological characteristics presented by the tumors in this series warrant the statement that a "true" cylindroma is an epithelial tumor constituting a particular histological variety of the mixed tumor and deriving from the salivary seromucous tissue. Cylindromas, though possessed of relative cytohistological and cytostructural monomorphism, are to be regarded as potentially malignant because of their cellular richness, their tendency to recurrence, and the frequency with which they undergo malignant degeneration as compared with mixed tumors. Radical resection, or rather a combination of radical removal and radiotherapy, is therefore the treatment of choice for cylindromas, just as it is for malignant tumors, because a definitive cure cannot be obtained by simple enucleation or irradiation alone.

Experimental Studies on Bacterial Contaminations of Bank Blood: III. The Survival and Growth of Bacteria in Bank Blood Incubated at 37 C. for Short Periods Before Refrigeration. P. Gellar, L. Chandler and E. Jawetz. J. Lab. & Clin. Med. **49:**573-582 (April) 1957 [St. Louis].

A small percentage of bank bloods will become contaminated with bacteria during collection in spite of the most rigid safeguards. While it is generally true that most fresh whole blood specimens kill or suppress the growth of a variety of bacteria, the earlier premise that contamination would be so attenuated as to be completely innocuous has been amply disproved by a number of serious or fatal reactions due to heavily contaminated blood. Many different antiseptic agents have been added to banked blood to prevent bacterial contamination, but none were completely satisfactory. Recent investigations with antibiotics appear more promising, but additional studies are necessary. During the course of previous studies on banked blood contamination, the authors inoculated coliform bacteria into fresh blood noted that the number of viable bacteria dropped sharply when the blood was allowed to remain at room temperature for 1 hour prior to refrigeration. This finding suggested the possibility that the natural antibacterial activity of fresh whole blood might be enhanced by incubating the blood at 37 C (98.6 F) for brief periods before the blood was refrigerated. Studies were carried out on the survival and propagation of various types of gram-negative bacteria in such incubated specimens. The gram-negative bacteria were divided into 2 groups, the "warm-growing" and the "cold-growing" on the basis of their characteristics in broth at 37 C (98.6 F) and at 4 C (39.2 F).

The authors were able to demonstrate that the natural antibacterial properties of fresh whole blood may be enhanced by incubation at 37 C for brief periods prior to storage of the blood at 4 C. Such incubation was much more effective in ridding the blood of those bacteria that grow best at 37 C than it was in ridding it of organisms that grow more rapidly or exclusively at lower temperatures. This apparently anomalous finding may be explained by a combination of 2 effects: the activity of specific antibacterial blood factors and the influence of low temperatures on bac-

terial growth. The authors used 27 different blood samples for this investigation. They found that with small inoculums of cold-growing bacteria, growth in the incubated samples was frequently delayed for 7 days or more, but, by the end of 21 days, large numbers of organisms were almost invariably present. Any given blood suppressed the growth of different strains of bacteria to a different degree, and no dependence could be placed on any sample to eliminate a particular chance contaminant. Storage of banked blood at refrigerator temperature is not in itself an adequate means of inhibiting all types of bacterial growth or of insuring sterility of the blood.

Study of Hemoglobinogenesis Through Alkali-Denaturation Test: Clinical and Experimental Observations in Intoxication Caused by Carbon Monoxide. C. Giordano and A. Guarino. Folia med. **40**:15-23 (Jan.) 1957 (In Italian) [Naples].

The effect of carbon monoxide on hemoglobinogenesis was studied in 20 subjects who in their work were chronically exposed to carbon monoxide. All subjects received an alkali-denaturation test. Experiments were also carried out on 2 groups of rabbits exposed to carbon monoxide. The results showed that of the 20 subjects all with marked carboxyhemoglobinemia, 3 had high levels of alkali-stable hemoglobin. These 3 subjects had at some time during their life had acute episodes of carbon monoxide poisoning. The experiments on rabbits showed that, in subacute carbon monoxide poisoning, the hemoglobin level is increased for a period of 50 to 60 days.

Sunlight as a Cause of Melanoma: A Clinical Survey. H. O. Lancaster and J. Nelson. M. J. Australia **14**: 452-456 (April 6) 1957 [Sydney].

A survey was carried out to ascertain whether environmental factors, especially sunlight, or certain bodily characteristics, such as fair skin, are of importance in the etiology of melanoma. On the same day a patient with melanoma was interviewed, 2 other patients were interviewed. These controls belonged to the same sex and age groups, and, in each pair, 1 had a basal cell carcinoma, squamous cell carcinoma, or keratosis of the skin, while the other had leukemia or cancer in some site other than the skin. Of the 173 patients with melanoma studied, 67 were men and 106 were women. There was an excess of red-haired and of fair-haired persons among these patients as compared with the other 2 groups. As regards the color of the skin, there was a larger proportion of fair-skinned types among the patients with melanoma and with other forms of skin cancer than among those with cancers in other sites. There were also more persons with blue and green-grey eyes among the patients with melanoma and skin cancer than among those with other forms of cancer.

A summary of sun exposure was devised by assigning scores to a number of factors and giving a total of these scores. The factors considered were length of time of living in Australia, occupational exposure, industrial hazards, war service, and the various sports. Of the patients with melanoma, 26.6% had experienced what was judged to be excessive exposure to the sun, as compared with 21.4% of the patients with skin cancer and 16.2% of the patients with other cancers. In discussing the reasons why the evidence in favor of both melanoma's and skin cancer's being caused by exposure to light was not more definite in this survey, the authors point out that there are associations with coloring and that an imporant association between skin color and exposure to sun probably exists, for a person with a fair, easily burned skin will probably not be exposed to so much sun as a dark-complexioned person who has no reason to fear exposure to the sun, since he does not burn easily. This association is probably responsible for making the differences in exposure between the various groups less than they would otherwise have been. The survey revealed that melanoma tends to occur in those with fair skin and to be more frequent in those who have been exposed to excessive doses of sunlight.

Bacteria Found in the Air Over the Atlantic Ocean. C. D. Kelly and S. Layne. Canad. J. Microbiol. **3**:457-460 (April) 1957 [Ottawa, Canada].

Since 1947, aerobiological studies have been carried out on the micro-organisms in arctic and nonarctic parts of Canada, Alaska, and over the Arctic Ocean. The fungi and bacteria found were apparently of soil origin. The results of examinations at different periods of the year indicated that in time the micro-organisms died and the air eventually became sterile. Air that had been over the arctic for a long time and winter air carried only small numbers of the more resistant types of micro-organisms. Fungi in such air were few in numbers or absent, indicating that they have a lower resistance than the bacteria. The sporeformers showed the greatest resistance and at times were the only organisms present.

This report is concerned chiefly with the aerobiological studies carried out during 2 sampling flights, over the Atlantic Ocean between Montreal and London in June and August, 1951. At 8,000 to 9,000 ft., the numbers of bacteria in the Atlantic air were low and average counts per cubic foot varied from 0.0 to 0.5 in polar air masses and 0.3 to 0.9 in tropical air. The fungus counts were somewhat higher, being 0.05 to 2.6 per cubic foot in polar air and 0.2 to 9.0 in tropical air. Isolation and classification of the bacteria revealed that those over the Atlantic were much like those found over land and included the following genera: Pseudomonas, Flavobacterium, Achromobacter, Corynebacterium, Micrococcus, Sarcina, and Bacillus. Since it was believed that groups of similar organisms would give as much information as would the species completely classified, the bacteria are reported as gram-negative rods, gram-positive pleomorphic rods, micrococci, and sporeformers. The ratio of the types of bacteria could be used to some extent to trace the history of an air mass. The tropical air tended to show a higher percentage of gram-negative rods and gram-positive pleomorphic rods than of micrococci and sporeformers, while arctic air tended to show the opposite.

BOOK REVIEWS

Atlas of Neuropathology. By Nathan Malamud, M.D., Associate Clinical Professor of Psychiatry and Neuropathology, University of California, San Francisco. Cloth. $20. Pp. 468, with illustrations. University of California Press, Berkeley 4, 1957.

In this impressively large and handsome volume, the author attempts a comprehensive visual presentation of the gross and microscopic features of neurological disease. The first of 10 sections comprising the main body of the book is a general description of the cytology and cellular pathology of the nervous system with 15 colored cuts illustrating as many straining methods and 37 black and white representations of typical pathological changes in neurons, nerve fibers, glia, and connective tissue. The remaining nine sections cover, in order, inflammatory, toxic and nutritional, demyelinating, vascular, traumatic, degenerative, neoplastic, and developmental disorders, with a final section on the sequelae of paranatal and postnatal pathological conditions. In his preface, the author states that "equal space has been given to all categories, but special attention has been paid to neglected conditions such as the heredodegenerative disorders and those pertaining to geriatrics, cerebral palsy and mental deficiency." A case method of presentation is used throughout, with a brief clinical abstract of a specific case followed by a description of the chief gross and microscopic features, illustrated by several black and white photographic reproductions of appropriate preparations. Text and illustrations face each other on opposite pages. The book concludes with a bibliography and an adequate index. This imposing and attractive volume, with nearly 1,000 photographs of gross and microscopic preparations, excites at first glance one's enthusiastic expectation. The illustrations are models of excellence, the typography, arrangement, and format are admirable, and the prose clear. The text and illustrations cover the field well. No important diseases are omitted.

These virtues, however, are not sufficient to make the work the comprehensive and definitive atlas of neuropathology that its beauty and size lead one to expect. No atlas can reflect all the nuances of neuropathological changes. In addition, the case method of presentation has few advantages and does not lend itself to thorough exposition of the manifold features of disease. Even within these limitations, some of the deficiencies of this book are surprising. Unfortunately, the coverage is superficial and sketchy and much is lacking in basic and important detail. For example, of 18 illustrations depicting the features of general paresis, only one myelin sheath stain is presented, and there is no description of the myelin destruction in the cortex and adjacent white matter. Also, there is no mention of the independence in this disease of the infiltrative process in the pia-arachnoid and that in the cortex or of the independence of the infiltrative and parenchymatous changes. Again, in the discussion and illustration of Huntington's chorea, the cortical changes are presented in only the most elementary and superficial fashion. In a half page of text on progressive lenticular degeneration (Wilson's disease), no mention is made of the deposition of copper in the brain and no photomicrographs of copper-containing tissues are shown. The Kayser-Fleischer ring is described as a characteristic pigmentation of the cornea with no suggestion that deposits of copper are responsible. This lack of important detail runs generally throughout the book. Furthermore, the text is surprisingly brief and almost exclusively descriptive, with no concern for the dynamics of disease. Such defects certainly reduce the book's value to the neuropathologist and make its use hazardous even for the beginner in that field, unless he supplements it with more authoritative and thorough textbooks and guides.

The Doctor, His Patient and the Illness. By Michael Balint, M.D., Visiting Professor of Psychiatry, College of Medicine, University of Cincinnati, Cincinnati. Foreword by Maurice Levine, M.D. Cloth. $7.50. Pp. 355. International Universities Press, Inc., 227 W. 13 St., New York 11, 1957.

In Great Britain "a large number of psychiatrists are either hostile to any kind of psychotherapy . . . or if they are not hostile they are interested only in physical methods, such as shock treatments, brain operations, and the ever increasing number of drugs." Yet "the more one learns of the problems of general practice, the more impressed one becomes with the immense need for psychotherapy." This new book is directed essentially to the resolution of this frustratingly paradoxical situation.

Avowedly, it is a critical report on a research project conducted at The Tavistock Clinic by a team of 14 practitioners and a psychiatrist who met once weekly for two or three years to study "the pharmacology of the drug 'doctor.'" In effect, however, the book is much more than a research report. It presents an instructive number of treatment records, submitted by the participating physicians, each record showing what the physician did with, to, and for the patient and what the research group thought thereon—all this with unsparing frankness. The author expands on these reports and their "group analysis" to argue a number of issues. Thus, each patient's illness incorporated some psychopathological components, and, as a result of treatment, the patient fared ill or well, according to the competence of the physician to recognize and to deal with these components. The general practitioner, according to the author, should exercise psychiatric awareness in his assessment of given patients and possess adequate skills to do requisite psychotherapy; lest he go beyond his depth, he should also know when and how to start and when and how to stop. These matters are treated at length. The author raises many more questions than he can answer defi-

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

nitely or illuminate clearly. The problems involved are complicated, but the author has not adequately differentiated between the gestaltism of the physician as a somatotherapist and as a psychotherapist, nor has he provided any criteria to help the general practitioner differentiate between what he can and should attempt in psychotherapy and what he must leave to the expert.

In spite of this, the book is a work of truly major significance. It is a penetrating, frank, stimulating, and instructive critique of present-day medical practice. It is an earnest and courageous assault on a major problem. This is a work to be read by the general practitioner, the medical educator, and the psychiatrist. Also, those interested in learning how medicine is practiced in Great Britain under the National Health Service will find this book most revealing.

Occupational Diseases of the Skin. By Louis Schwartz, M.D., Louis Tulipan, M.D., and Donald J. Birmingham, M.D., Medical Director, Chief Dermatologist, Occupational Health Service, U. S. Public Health Service, Cincinnati. Third edition. Cloth. $18. Pp. 981, with 191 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1957.

This is the third edition of what has come to be the standard textbook on occupational diseases of the skin. This edition appears 10 years after the second and has been brought up to date. Three new chapters have been added: an interesting discussion on occupational marks by F. Ronchese; another on skin hazards from radiation in atomic industry, medicine, and defense by W. D. Norwood; and one on skin hazards of detergents and surface-active agents by Anthony M. Schwartz. This book is a complete source of information on occupational dermatoses and related matters. There is coverage of practically every kind of industrial contact that one is likely to encounter. There are chapters considering the dermatoses caused in various industries and those caused by contact with a wide variety of substances; finally, there is an analysis of many occupations considering what particular occupational hazards are associated with each. There is also a discussion of the medicolegal aspects of occupational dermatoses. There are many useful lists and tables, such as a list of plants and woods that have been known to cause irritation, a list of patch test concentrations, and a list of known chemical irritants. This book is indispensable to any physician who deals with industrial dermatosis. It should also be of value to anyone, physician or otherwise, who has to do with plant hygiene.

Modern Trends in Geriatrics. Edited by William Hobson, B.Sc., M.D., D.P.H., Professor of Social and Industrial Medicine, University of Sheffield, Sheffield. Cloth. $13.50. Pp. 422, with 68 illustrations. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33rd St., New York 16, 1957.

In his introduction, the editor points out that geriatrics has been a neglected subject because the medical profession, in general, has been of the opinion that not much help could be given the elderly. The medical problems of the aging have been regarded as of minor importance when compared with, for example, the problems of child health. Geriatric medicine is now becoming recognized as a major field of medical study. The elderly, like the young, have anatomic, physiological, and pathological features peculiar to their age. There is little of specific value in standard medical books on these subjects. There is practically nothing of any importance on the normal variations that occur with passing time. In this volume the most important aspects of the health and medical problems of the elderly are discussed. There is an excellent short bibliography at the end of each chapter.

The list of authors of the various chapters reflects care in selection and in ability to summarize the literature of their particular subject. The authors are British and their discussions reflect the rapidly increasing amount of research being conducted in geriatrics in Great Britain. There is an excellent article on aging from a biological and cellular point of view by Geoffry H. Bourne. This article contains a classification of cells according to the aging process. There are a number of illustrations. An important discussion of the normal values and the interpretation of biochemical data of the elderly is presented by Arthur Jordan. The contribution on arteriosclerosis and hypertension by F. H. Smirk reflects a rich experience in clinical medicine with hypertensive patients. In a small book of this kind, it is not possible to include all aspects of aging. There is no exhaustive presentation of the psychiatric problems of the elderly, but, in the chapters on home care and also that of hospital care of the elderly, reference is made to the importance of emotional problems. This volume should be required reading for faculties of medicine, interns, residents, and general practitioners. The time has come when more attention and study must be directed to the problems of our aging population.

Blood Transfusion in Clinical Medicine. By P. L. Mollison, M.D., M.R.C.P., Director, Medical Research Council's Blood Transfusion Research Unit, London. With foreword by Sir Alan N. Drury, C.B.E., F.R.S. Chapters on blood groups revised in collaboration with Marie Cutbush, B.Sc. Second edition. Cloth. $9. Pp. 587, with 80 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

Most of the chapters in the second edition of this textbook have been rewritten in order to include the many advances made in this field in the past five years. The various chapters deal with the taking and storing of blood, survival after transfusion, blood volume, hemorrhage, anemia, methods of estimating the survival time of red blood cells in vivo, results in normal subjects, diminished survival of red blood cells in disease, ABO blood groups, the Rh groups, other blood group systems, interactions between red blood cells and their own serum or plasma, the reactions of red blood cells and serum "changed" by bacteria, blood grouping techniques, incompatibility or shortening of the life-span of red blood cells by isoantibodies, investigation of hemolytic transfusion reactions, other unfavorable effects of transfusion, some normal blood findings in newborn infants, indications for simple transfusion, placental transfer of antibodies, and hemolytic disease of the newborn infant. The chapters contain detailed information and instructions in technique. A lengthy bibliography is included. The book is highly recommended.

QUERIES AND MINOR NOTES

SEASONED FOOD FOR INFANTS

To the Editor:—*Is it all right to feed seasoned puréed foods from the table to infants?*

H. J. Jacobs, M.D., Spring Valley, Ill.

This inquiry has been referred to two consultants, whose respective replies follow.—Ed.

Answer.—This question could be answered more concisely if the nature of the seasoning and the ages of the infants were defined. While puréed foods can be fed infants under 3 months of age, nutritional requirements can be met just as adequately during these months without such supplementation. Hence, the consensus of authorities in the field of infant nutrition is that mothers should not be asked to expend the time required for such spoon feeding (Butler and Wolman: *Quart. Rev. Pediat.* **9**:63, 1954). As infants should be getting milk or milk substitutes in amounts that cover their sodium and chloride requirements, salting food is not essential and oversalting may be undesirable. Puréed foods for the family as usually seasoned in this country are all right for infants over 6 months, but curry and hot tamale should not be included.

Answer.—None of the flavoring or seasoning agents in common use, other than table salt, are apparently needed in the diet of young infants—certainly not during the early months when they seem to require and prefer puréed foods. Feeding the baby on puréed leftovers is not to be recommended. Such foods are too likely to be inferior, owing to vitamin deterioration and bacterial growth, irrespective of whether they are seasoned or not.

When the time comes to give table foods (which generally means foods that are not puréed), there is no apparent necessity to exclude foods which are moderately or normally spiced, since there is no evidence in the medical literature that such foods are harmful. The child may or may not like the foods as seasoned for the family. If he does not, then he solves the problem very nicely for himself by simply refusing to eat them. Recent researches by Schneider and associates (*Am. J. Gastroenterol.* **26**:722, 1956) indicate that many spices are permissible even in the diets of patients with gastric ulcer. Another recent report on "Peptic Ulcer Therapy" by C. A. Marshall and associates tends to confirm the observations of Schneider.

SPLITTING NAILS

To the Editor:—*Is there any evidence that pantothenic acid is of value for splitting nails?*

S. Theodore Sussman, M.D., New Rochelle, N. Y.

Answer.—There are no reports or any clinical evidence that pantothenic acid is of value for splitting nails.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Annonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

LYSINE IN METABOLISM

To the Editor:—*What is known of lysine in human metabolism? What function is it thought to have, what is thought to be the minimum daily requirement, and what foods contain the most lysine? Can it be obtained in tablet, powdered, or liquid form as such? How toxic is it? What quantities can be eaten with no danger to humans, and what would be the signs and symptoms of toxicity?*

H. Curtis Wood Jr., M.D., Philadelphia.

Answer.—The amino acid lysine is one of the constituents of most proteins. It is dibasic, as it contains two amino groups but only one carboxyl group. In pure form it usually is prepared as the monohydrochloride. Only the L isomer exists in natural foods and is metabolized in man. It is present in considerable quantities in most foods, composing for example 7.2% of the amino acids in whole egg protein, 8.1% of beef muscle, 3.3% of oats, and about 2.7% of whole wheat protein. Milk, fish, and most other animal foods are good sources of lysine. Some vegetables and fruits, although containing little protein, may add significant quantities of lysine to the diet.

Lysine cannot be synthesized in the body and therefore has been called "essential," as demonstrated in the experiments by Rose (cited in *Nutrition Rev.* **14**:232, 1956). In contrast to most other amino acids, lysine does not enter into the "dynamic equilibrium" described by Weissman and Schoenheimer (*J. Biol. Chem.* **140**:779, 1941). Many of the so-called essential amino acids can be replaced by closely related compounds, but lysine cannot, so that it has been spoken of as "the most specifically indispensable of the amino acids." As an essential amino acid, lysine is required for maintenance of nitrogen balance in adults, growth, and for healing of wounds and regeneration; that is, it is required for protein synthesis as one of the essential amino acids. The minimum requirement for lysine by the healthy adult is stated by Rose to be 1.6 Gm. per day, although he has suggested a recommended daily allowance of 3.2 Gm. (cited in *Nutrition Rev.* **14**:232, 1956).

Little is known concerning toxic effects of lysine in man. Supplementation with lysine depresses growth of experimental animals on deficient diets. In fact, the addition of other individual amino acids has been reported several times to produce deleterious effects on laboratory animals (Elvehjem and Harper: Council on Foods and Nutrition, *J. A. M. A.* **158**:655 [June 25] 1955). Vegetable (especially cereal) diets are somewhat lower in lysine than those containing animal products but should be supplemented with lysine. Further research will be necessary to assess the relative importance of the administration of lysine and other amino acids and the possible harm from so doing.

TREATMENT OF URTICARIA

To the Editor:—*Is there anything new in the treatment and management of chronic intractable urticaria? What is the status of histamine desensitization as a treatment?*

Henry Fisketti, M.D., Duluth, Minn.

This inquiry has been referred to two consultants, whose respective replies follow.—Ed.

Answer.—An effort should be made to find the etiology of a given case. Treatment of urticaria should be based whenever possible on the cause. In about 40 to 50% of the cases, urticaria has an allergic etiology. Allergy to intestinal parasites is occasionally encountered. Psychosomatic factors are not infrequently also of importance. Antiallergic drugs, antihistamines, and steroids may be used for limited time periods. Histamine "desensitization" does not have a logical basis in the treatment of urticaria.

Answer.—There is no recent change in the treatment of chronic urticaria. In some, an extrinsic allergic factor can be demonstrated. This is usually a drug or food or at times a persistence from a penicillin reaction. The general belief also prevails that some cases are caused by foci of infection, such as tonsils, gallbladder, or prostate. In some cases, parasitic infestation (tapeworm, Ascaris) may be responsible. In a very large percentage, however, no allergic or other proved etiological factors can be demonstrated. For this group various explanations have been offered, such as psychosomatic or intrinsic. Injections of histamines have been used in urticaria. Their efficacy is in doubt. It is established that one cannot desensitize to histamine, i.e., the dose tolerated at the beginning of treatment is the same as at the end of a series of injections. Treatment of chronic urticaria consists in some of the elimination of allergic or infectious causes. Where no cause can be found, nonspecific therapy, such as the injection of typhoid vaccine or similar measures, is used by some. For palliative relief, antihistamines are employed, at times with the addition of ephedrine. The use of cortisone, prednisone, or corticotropin is justified only in the severe cases.

LEAD POISONING IN AN INFANT

To the Editor:—*Can a 17-month-old infant have lead poisoning, as evidenced by lead lines at the epiphysial ends of the long bones, from inhalation of paint sprays?*

Joseph M. Klein, M.D., Wilkes-Barre, Pa.

Answer.—It is difficult to conceive of a 17-month-old infant having exposure to lead through the medium of paint sprays. Few spray paints now contain lead, and, apart from industry, paint spraying usually is only an occasional activity. A 17-month-old infant could have lead poisoning, but currently the common source is scaled-off lead paint from interior woodwork in homes. The best means for diagnosis resides in quantitative lead determinations in blood and urine. Epiphysial line abnormalities may be present but are not diagnostic of lead deposition. Similar x-ray disclosures may arise in healing rickets and in connection with restoration of calcium level after other nutritional disorders. If the epiphysial line abnormalities are present and if an exposure to lead has been established, then such bony changes could result from the deposition of lead compounds in the epiphysial areas. In addition, some changes may arise at the margins of flat bones. Rings of modified bony density may appear in the ossification centers of cartilage. The intensity or breadth of the bands or lines is influenced to some degree by the duration of lead exposure and the quantity of lead taken into the body. Diagnostic methods other than these x-ray changes should be pursued.

OSTEOARTHRITIS OF THE KNEE

To the Editor:—*Please supply information on the latest treatment of osteoarthritis of the knee joints and lower lumbar region of the back. A patient, aged 72 years, was hospitalized two months ago for severe pain in the back and knee joint after a slight fall. X-rays showed some pinching of fourth lumbar nerve and moderate changes in the knee joint due to changes in bone structure from this arthritis. The patient's laboratory blood tests were negative, except for some slight elevation in the sedimentation rate. Her kidneys and heart appeared normal. Blood pressure was 160 to 170 mm. Hg systolic. After a two-week stay at the hospital, the patient's backache and pain in the knee joint disappeared. Now she has some discomfort or slight shooting pain in the knee joint, about an area of 3 sq. in. at the inner portion of knee joint, and some tenderness of the fourth lumbar nerve from the inside of the thigh to the knee joint. Most of the pain is at the inner portion of the knee joint, and there is some inflammation around this joint. This trouble began the middle of September, 1956, and at the time of writing there has not been any change in this condition in the last 14 weeks. The patient has been receiving infrared treatment with hot compresses.*

M.D., Connecticut.

Answer.—Osteoarthritis of the knees may be treated effectively and with marked relief of symptoms by injecting hydrocortisone into the joints. This can be done without local anesthesia. A 24-gauge, 2-in. needle should be used. It should be introduced at the anterior medial margin of the knee joint. The point of the needle should be within the joint. Two cubic centimeters of hydrocortisone should be injected into each joint. Each injection should be followed by a program of restricted activity. This means that the patient should not do any walking that is not essential to her daily activities. She should have the infrared treatment or the application of moist heat and massage to the knees daily.

The backache and irritation of the fourth lumbar nerve root will be helped by sleeping in the "contour" or Williams position. Most furniture dealers can sup-

ply the contour chair. A hospital bed with a Gatch frame can be rented and adjusted for sleeping so that the hips and knees are flexed 35 degrees and the shoulder or back rest is elevated to an angle of 35 degrees. This position relaxes the ligamentous structures of the lower back, enlarges the neural foramens, and relieves crowding or pinching of the fourth nerve root. The application of heat and massage to the lower back is of value in dealing with backache of this type. Treatment with infrared heat or hot compresses should be followed by massage.

ALLERGY TO THYROID MEDICATION

To the Editor:—*A patient had a subtotal thyroidectomy in 1953 because of a benign adenoma. Shortly thereafter her hair and skin became very dry and her nails brittle, and there was marked puffiness of the lower lids. Dessicated thyroid extract, 3 grains (0.2 Gm.) daily, relieved the condition, but about six months ago she developed a severe case of allergic rhinitis. This was relieved somewhat by withdrawal of the thyroid extract, and it promptly recurred when administration of the thyroid extract was started again. Since then she has been taking sodium levothyroxine (Synthroid), 0.2 mg., with considerable relief of the rhinitis and of the puffiness of the lids and the dryness of the skin, but her hair is very dry and difficult to wave. Any general information as regards treatment will be greatly appreciated. What are the relative values of the basal metabolism test and the serum protein-bound iodine determination? Are there any particular indications for either or both?*

Erwin E. Stephens, M.D., Redlands, Calif.

Answer.—The clinical symptoms appearing after a subtotal thyroidectomy certainly suggest a hypothyroid state, and the relief of symptoms after administration of thyroid extract and sodium levothyroxine support this conclusion. If laboratory confirmation of the hypothyroidism is desired this can be accomplished best by a determination of the serum protein-bound iodine level after all specific medication has been discontinued for about one month. Values below 3.5 mcg. per 100 ml. suggest hypothyroidism. An elevated cholesterol level is also to be expected. The protein-bound iodine determination is probably of greater value than the basal metabolism rate. Techniques using radioactive iodine are not generally of great use in suspected hypothyroid states. If thyroid extract or thyroxine are used in treatment, the protein-bound iodine determination can be used to control the dosage level. If triiodothyronine is used, the protein-bound iodine levels are not raised by the drug, although the hypothyroidism is relieved.

Allergic reactions to thyroid extract are very infrequent but may occur. It is possible that a change in the brand used may give relief, or an antihistaminic drug may be given to suppress the allergic response. There are no special suggestions with regard to the dryness of the hair if sufficient thyroid is given to control the other symptoms of hypothyroidism.

TOXICITY OF ANTIHISTAMINICS

To the Editor:—*Please supply information concerning a certain patent cough medicine that contains the following ingredients per fluid ounce: Phenylpropanolamine hydrochloride, 1 grain (60 mg.); methapyrilene fumarate, 1.5 grains (0.1 Gm.); sodium salicylate, 20 grains (1.2 Gm.); ammonium chloride, 10 grains (0.6 Gm.); chloroform, 2 min.; and alcohol, 6%. A patient, who was seven and one-half months pregnant, took this preparation for two days preceding an intrauterine death in the following amounts: 4 tsp. the first day and 3 tsp. the second day. Is there any material in this preparation sufficiently toxic to cause fetal death?*

A. D. Heetderks, M.D., Bozeman, Mont.

Answer.—Methapyrilene fumarate is an antihistaminic agent of relatively low toxicity with few, if any, undesirable side-reactions. It also possesses mild local anesthetic properties. There have been no reported cases of fetal death after maternal ingestion of this substance. Accidental ingestion of 100 mg. by a 16-month-old child resulted in death presumably secondary to nephron nephrosis. The patient mentioned in the inquiry received 45 mg. the first day and 34 mg. the second. This dosage is well below that recommended therapeutically, a maximum dose not to exceed 400 mg. per 24 hours.

Phenylpropanolamine hydrochloride is an ephedrine-like compound having longer vasoconstrictor action than ephedrine but less likelihood of producing excitation and nervousness. The recommended dose for adults is 25 to 50 mg. every three or four hours. The patient in question received 30 mg. the first day and 20 mg. the second day. The other ingredients contained in this cough medicine, namely, sodium salicylate, ammonium chloride, chloroform, and ethyl alcohol, are not considered toxic in the doses involved here. In the absence of a severe sensitivity reaction in the mother, as manifested by cyanosis, convulsions, or cardiorespiratory depression, it is exceedingly unlikely that there was any cause-and-effect relationship between the ingestion of the cough medicine and the subsequent fetal death.

SENSITIVITY TO THIOGLYCOLATE

To the Editor:—*A patient developed acute glomerulonephritis. Her previous health was good, and there was no evidence of possible infectious origin. The patient handles beauty products in her work (for example, cold-wave preparations and dyes), some of which have been considered as possible chemicals injurious to the kidneys. What are the active ingredients of these agents, and what is the occupational hazard, if any, of using them constantly?*

Joseph Aspel, M.D., Philadelphia.

Answer.—At the present time the greater number of cold-wave solutions represent thioglycolates or some compound of thioglycolic acid. No cold-wave solution may be expected to be the direct cause of infections. The greater portion of investigative work centering about thioglycolates and cold-wave solutions has re-

lated to home permanents, thus involving fairly weak concentrations of such substances as the sodium or the ammonium thioglycolate. Such watery solutions approximate 3 to 5%. Apart from some possibility of skin sensitization, it is not known that this strength of cold-wave solution has been proved to be detrimental to the home user on either a local or a systemic basis. The situation as to the professional applicator of cold-wave solutions may be different. The strength of solution may be appreciably higher, and obviously exposure may be repeated during the day, and certainly many times during the week or month, for many operators.

Although the sensitizing properties of the thioglycolates are low, some sensitization has been established. In the midst of conflicting claims, statements by Brunner (*A. M. A. Arch Dermat. & Syph.* **65:** 316-326 [March] 1952) are impressive: "Ammonium thioglycolate has an exceptionally low sensitizing index; in general, where sensitization does develop it is of the eczematous-contact-dermatitis type. Hair damage may occur in some instances in which the hair has been previously altered by dyes and bleaches, particularly when directions for use are not followed and over-long processing times are employed. Such damage is apparently limited to the hair shaft, and no inhibition of growth is observable. Direct systemic toxic manifestations were not seen after percutaneous application of ammonium thioglycolate." The professional beauty-parlor operator consistently is exposed to many chemicals other than the thioglycolates, such as sodium bromate employed as the neutralizer for the thioglycolate waving solution. The multiplicity of exposures makes it difficult to establish any precise offender, particularly as to sensitization or direct skin irritation.

ANDROGEN-ESTROGEN THERAPY

To the Editor:—*Should a man past 76 years of age, who had a transurethral resection 10 years previously and who is without present sexual desire (a condition which has existed for several years) take a capsule containing methyltestosterone, 1.67 mg., and Theelin, 0.167 mg., three times a day?*

M. L. Brakebill, M.D., Sharon Springs, Kan.

This inquiry has been referred to two consultants, whose respective replies follow.—Ed.

Answer.—Combined androgen-estrogen therapy may be beneficial to a man 76 years old in relieving nervous symptoms, fatigue, and depression. Such therapy may promote storage of calcium, phosphorus, and protein. Hormone treatment, however, is not often successful in restoring libido or potency. When such treatment is used in elderly patients, it is usually best to carefully explain to the patient that the treatment is employed to promote general strength and health and is not intended specificially to increase sexual desire or performance.

Answer.—There can be no harm in a man past 76 years of age taking a capsule containing methyltestosterone, 1.67 mg., and Theelin, 0.167 mg., three times a day. The amounts are so small that they probably would not do him any harm. However, it has been discovered that the activity of prostatic malignancy is affected by the intensity of androgenic stimulation, and should this man have such a nidus, it is strongly advised that no androgenic therapy be used, no matter how small the dose is. A local medical man should examine the patient's prostate at frequent intervals to note whether there is any change in consistency of the gland.

COEXISTENCE OF INTRAUTERINE AND EXTRAUTERINE PREGNANCY

To the Editor:—*A 37-year-old patient was recently operated on for a ruptured ectopic pregnancy of the left tube because of severe hemorrhage. She also had a uterine pregnancy of the same gestation. A subtotal hysterectomy, with removal of the fetus, was done to acquire positive control of the bleeding. What is the frequency of twin uterine and extrauterine pregnancy?*

W. C. Dodds, M.D., Detroit Lakes, Minn.

Answer.—The coexistence of intrauterine and extrauterine pregnancy is not common. Reeves and Savarese (*Obst. & Gynec.* **4:**492, 1954) state that there are 421 cases of simultaneous intrauterine and extrauterine pregnancies reported in the literature. It is important to differentiate "combined" from "compound" intrauterine and extrauterine pregnancy. "Combined" intrauterine and extrauterine pregnancy means the existence of simultaneous pregnancies, whereas "compound" intrauterine and extrauterine pregnancy refers to the superimposition of an intrauterine pregnancy on a previous extrauterine pregnancy, generally a lithopedion.

TREATMENT OF HEMANGIOMA

To the Editor:—*A 4-year-old girl has a recurrent strawberry hemangioma on her forearm. This was present at birth and was increasing in size until she was one year old, at which time it was treated with radium and completely disappeared. There are now streaks of apparent recurrent hemangioma appearing in the old scar (the old scar is a pale area in the skin about 2 cm. in diameter). Should this recurrent lesion be treated or observed with hopes for its spontaneous disappearance?*

John S. Argue, M.D., Pittsfield, N. H.

Answer.—From the description, immediate treatment is not imperative. In a patient 4 years of age, such lesions are not particularly responsive to radiation or cryotherapy. Injection of sclerosing substances should not be used unless the lesion is cavernous and deep. Therefore, surgical excision is the only possible treatment, and this can be performed at any time. From the description (pale scar with streaks of apparent recurrent hemangioma), however, one must consider the possibility of a developing radiodermatitis with telangiectasia. If this is the situation, excision at this time is indicated.